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THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

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EDITORIAL

THROUGH the past several years the *News Letter* of the Canadian Anaesthetists' Society has served to keep the members informed of the affairs of the Society, and in touch with the activities of their colleagues across Canada. During the past two years the publication of the *Proceedings* of the Society, containing papers presented at formal meetings of the Society and of its Divisions has been well received, and has, we believe, been of great value particularly to those members who have been unable personally to attend the meetings at which these papers were presented. The decision of the Council to combine these two publications into a single quarterly journal should provide a publication of yet greater value to Canadian anaesthetists, and of interest to practitioners of the specialty of Anaesthesia beyond our borders. This journal will provide a suitable Canadian medium for the presentation of original work by Canadian anaesthetists and a means of communicating our news and views to our Canadian colleagues, and to others who may take some interest in them. Given the continued support of the anaesthetists of Canada, our new publication should maintain the standard of excellence set by its two predecessors.

PENDANT les quelques dernières années la *News Letter* de la Société Canadienne des Anesthésistes a servi à renseigner les membres sur les affaires de la Société et à les maintenir en contact avec les activités de leurs collègues à travers le Canada. Ces deux dernières années la publication des *Comptes-Rendus* de la Société, comprenant les textes des conférences prononcées aux réunions officielles de la Société et de ses Divisions, a été bien reçue et a été, nous le croyons, d'une grande valeur, surtout pour ces membres qui n'ont pas pu assister en personne aux réunions auxquelles ces conférences ont été présentées. La décision du Conseil de combiner ces deux publications en un seul journal trimestriel, devrait fournir une publication d'une valeur encore plus grande pour les anesthésistes du Canada, et susceptible d'intéresser les spécialistes en anesthésie au-delà de nos frontières. Ce journal fournira un organe canadien approprié à la diffusion de travaux originaux d'anesthésistes canadiens et un moyen de communiquer nos nouvelles et nos opinions à nos collègues canadiens et à d'autres qui pourront s'y intéresser. Avec l'appui soutenu des anesthésistes du Canada, notre nouvelle publication devrait maintenir le niveau d'excellence établi par ses deux prédécesseurs.

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POULENC

THE USE OF SYMPATHOMIMETIC AMINES IN THE TREATMENT OF SHOCK*

JAMES G. FOULKS, M.D.**

ANY discussion of drug therapy must necessarily revolve around two key points:

(1) What is the nature of the derangement to be treated? An understanding of the underlying pathogenesis of a diseased condition is essential to the definition of rational therapeutic objectives, that is, to a determination of what changes are required in order to correct the disordered function.

(2) To what extent can the therapeutic objectives thus defined be met by available pharmacological tools? An adequate understanding of the actions of a drug is necessary to know whether or not its use can be expected to aid in overcoming a particular pathological condition.

These principles may seem self-evident, and yet the breadth of our ignorance in both of these areas often requires us to rely on an empirical rather than a rational basis for therapy. The past five years have witnessed a number of important advances in the pharmacology of the sympathetic nervous system, with the introduction of agents whose place in our therapeutic armamentarium is yet to be fully ascertained.

Among the sympathomimetic agents, nor-epinephrine has probably received more attention recently than any other. Actually, nor-epinephrine is not a new compound, its structure and basic actions having been known for nearly fifty years. Renewed interest in this compound has followed the relatively recent discovery that it is produced in the body and in fact is the major mediator of sympathetic nerve activity, comprising 80 per cent or more of the material released upon sympathetic nerve stimulation, the remainder consisting of epinephrine. Both of these substances are also present in the secretion of the adrenal medulla, but their relative proportions are reversed. The presence of 10 to 15 per cent of nor-epinephrine in extracts of the adrenal medulla was overlooked for many years, until its chemical separation became possible through the development of improved techniques.

While both epinephrine and nor-epinephrine are pressor compounds, their administration leading to a rise in blood pressure, nevertheless, there are a number of important differences in their cardiovascular actions. These can be appreciated most readily by a brief description of their effects on the heart and the peripheral circulation during continuous infusion.

The actions of epinephrine on peripheral vessels are mixed. While the vessels of the skin and the splanchnic bed are intensely constricted, this effect is more or less counterbalanced by dilatation of the vessels of the skeletal muscles, so that the total peripheral resistance is relatively unchanged. The cardiac stimu-

*Presented at a meeting of the British Columbia Division, Canadian Anaesthetists' Society, January, 1954.

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lating actions are therefore primarily responsible for the pressor response which results when epinephrine is administered in this fashion.†

Nor-epinephrine (Arterenol, Levophed®) while less potent in some of its vaso-constrictor actions, is more uniform. Its vaso-dilating actions are minor and its over-all effect is predominantly vaso-constriction with a rise in total peripheral resistance. Its cardiac stimulating action is almost as intense as that of epinephrine in isolated preparations, but in intact patients it is largely mitigated by reflexes arising from presso-receptors, which actually lead to a bradycardia by way of the vagal efferents to the heart. Thus the pressor response to nor-epinephrine is dominated by its peripheral vaso-constrictor actions.

These divergent actions serve to emphasize the point that the blood pressure is always the resultant of two components, cardiac action and peripheral vascular resistance, and an increase or decrease in either may be responsible for raising or lowering the blood pressure. This reciprocal relationship is further illustrated by the actions of isopropyl nor-epinephrine, a closely related amine with a marked vaso-depressor action. This compound causes a predominant vaso-dilatation with a marked fall in total peripheral resistance. Although its cardiac stimulating actions are, if anything, more intense than those of epinephrine and nor-epinephrine, and are unopposed by reflex modulation, the net effect is one of a substantial fall in blood pressure.

Current interest in sympathomimetic agents has been particularly aroused by the proposal that they may be efficacious in the treatment of shock. An evaluation of this possibility requires a brief consideration of some of the salient features of the various conditions grouped under the heading of shock. Broadly speaking, the principle feature which these conditions share in common is a persistent hypotension, the proximate cause of which may be either cardiac or peripheral. The obvious common-sense approach when faced with this situation, is to consider means of raising the blood pressure. The use of vaso-constricting drugs offers a convenient means to this end. However, this approach requires careful examination before it can be accepted as rational. Is the blood pressure a reliable measure of circulatory adequacy? Is *hypotension*, per se, the principle threat to life? The answer to this latter question must be qualified by saying that it depends on the degree. The crucial responsibility of the circulation is to provide oxygen and nutrition to the tissues. Its ability to do so is determined directly by the *rate of flow* of blood through the peripheral circulation, and while adequate flow depends upon a sufficient head of pressure, pressure is not the sole determinant of blood flow. The flow of blood through any tissue is determined by the resistance to flow offered by the tone of its small vessels as well as upon the head of pressure under which the blood is delivered. If vascular tone is reduced by vaso-dilatation, the pressure required to maintain a given flow through that tissue is also reduced. Actually, hypotension which is primarily peripheral in origin, that is, due to vaso-dilatation, is often well tolerated if not too drastic, even over fairly prolonged periods of time. For instance, high tran-

†This description is based on the work of Goldenberg *et al.* (Amer. J. Med. 5:792 (1948)) who used moderate infusion rates. Larger amounts of epinephrine may constrict the vascular bed of skeletal muscle as well.

section of the spinal cord in the cervical region gives rise to a condition known as spinal shock. This condition is characterized, among other things, by peripheral vaso-dilatation and a fall of mean blood pressure to levels of 30–40 mm Hg., which may persist for twenty-four hours or longer with no permanent deleterious effect. Similar tolerance to prolonged hypotension experimentally is manifested by animals subjected to continuous stimulation of the carotid sinus. This is the type of hypotension which is deliberately produced under controlled conditions for certain surgical procedures by means of the administration of ganglionic blocking agents. In sympathectomy and in adrenergic blockade by drugs, a similar hypotension of peripheral origin is produced which can be well tolerated, in the supine position at least. The absence of reflex control in these conditions may jeopardize the cerebral circulation if the erect position is maintained. The advantage of ganglionic blockade is that a pressor response can still be produced and maintained by the more peripherally acting sympathomimetic amines. The same thing is true of the shock which may occur in spinal anaesthesia and one wonders whether this condition is truly as grave as it is sometimes considered to be.

In contrast to these examples are those cases of shock which follow a marked reduction in circulating blood volume, such as that which occurs following haemorrhage, burns, certain types of trauma, surgical procedures, and other related conditions. The loss of circulating fluid leads to poor venous return, poor cardiac filling, and a primary reduction in cardiac output. Compensatory reflex tachycardia commonly occurs, but the heart cannot put out more blood than is returned to it. Compensatory reflex vaso-constriction is fairly intense (although not maximal) and during the initial stages blood pressure is often maintained at fairly normal levels, while the rate of flow through the tissues is reduced as a result of the reduced cardiac output coupled with compensatory vaso-constriction. If under these circumstances, blood pressures as low as 30–40 mm Hg. are allowed to persist for several hours, the shock becomes irreversible. While blood pressure may be restored temporarily, it cannot be maintained and the shock cannot be overcome, even after complete restoration of the lost circulating blood volume. Even the transfusion of relatively large amounts of blood is to no avail. We have already seen that in spinal shock such levels of pressure may be tolerated for long periods of time. It is not the low pressure which causes shock to become irreversible, but the reduced peripheral flow of blood through vital organs. The exact mechanism of irreversible shock is still not fully agreed upon, but the peripheral compensatory vaso-constriction appears to play an important role in its development. A number of investigators have reported that complete blockade of the sympathetic nervous system offers a highly significant degree of protection against the development of irreversible shock due to bleeding or trauma in experimental animals. Animals are subjected to shocking procedures and allowed to remain hypotensive for several hours, whereupon the volume of the circulating fluid is restored to normal levels. In control animals, survival rates range from 10 to 30 per cent. In animals pre-treated with sympathectomy, ganglionic or adrenergic blockade, and subjected to the same or equivalent procedures, recovery commonly runs as high as 80 to 90 per cent. It should be

emphasized that in these experiments the shock is carried to the stage of irreversibility by maintaining a predetermined degree of hypotension. Animals subjected to adrenergic blockade reach this point with a smaller degree of blood loss than do untreated animals. But untreated animals will survive a degree of blood loss greater than that which can be tolerated by animals subjected to adrenergic blockade.† Adrenergic blockade is not of therapeutic value in animals already carried to the irreversible stage of haemorrhagic shock. The point to be emphasized is that it is not the hypotension which leads to irreversibility, but the reduced flow of blood through vital tissues.

A considerable amount of experimental evidence has now accumulated which indicates that the release of ferritin (so-called VDM), especially by the anoxic liver, may play an important role in an explanation of these findings. This substance appears in the blood stream at about the time that shock becomes irreversible, and the liver loses its capacity to inactivate this material. Arterialization of the portal vein to the liver decreases the mortality of shock procedures. In animals pre-treated with sympathetic blockade, VDM does not appear in the blood during the maintenance of a degree of hypotension which would otherwise lead to irreversible shock, and the liver retains its capacity to inactivate this material. VDM acts primarily to dilate capillary beds, and to render them unresponsive. The dilated beds lead to pooling of the blood, and the reservoir thus created may soak up large quantities of transfused blood and render the restoration of *effective* circulating blood volume exceedingly difficult to accomplish. Capillary anoxia may lead to further fluid loss directly into the tissues. In shock, hepatic blood flow is substantially reduced and when the irreversible stage is reached, the resistance to flow in the hepatic bed remains high in spite of restoration of normal circulating blood volume.

These facts force us to recognize that the rational therapeutic objective in hypotension or shock is the maintenance of a flow of blood adequate to sustain the viability of such crucial organs as the liver, the kidney, the heart and the brain. While a minimal head of pressure is required for this purpose, particularly in the case of the heart and brain, the level required is apparently not large. In simple hypotension, the work required of the heart falls more rapidly than does coronary flow. There is a fair margin of safety in the cerebral circulation between the level of flow required to maintain normal consciousness, and that which will produce irreversible neuronal damage. We have already seen that in the case of the liver and kidney, vaso-constriction in the presence of an inadequate cardiac output jeopardizes rather than enhances the flow through these organs. As a matter of fact, even with a normal or elevated cardiac output, excessive vaso-constriction alone, if prolonged, may give rise to irreversible shock. Acute decerebration in animals is associated with a marked sympatho-adrenal discharge and within a few hours fatal shock develops. Shock can be prevented and survival greatly prolonged in such animals by sympathectomy or adrenergic blockade. Large infusions of pressor sympathomimetic amines alone will also precipitate shock in experimental animals, an outcome which can be prevented by

†More recently published studies have indicated that when bleeding is gradual, animals with adrenergic blockade require just as much blood loss to reach a given degree of hypotension and are not more sensitive to a given degree of blood loss.

adrenergic blockade. It is well known that factors such as pain, cold, strong emotions and asphyxia, all of which tend to produce reflex vaso-constriction, also tend to potentiate the development of shock from haemorrhage or trauma, and for a given degree of fluid loss tend to make traumatic shock more severe than that due to simple haemorrhage alone. Experimentally it has been shown that this potentiation in the case of strong afferent stimuli can be prevented by blockade or interruption of the nervous pathways involved.

All of these considerations make conservative medical scientists very wary of claims for beneficial effects of sympathomimetic amines in shock, particularly where the condition is the result of loss of circulating blood, and where fairly intense reflex vaso-constriction is already present. In the case of hypotension due to primary vaso-dilatation (spinal anaesthesia, spinal shock, ganglionic blockade, certain types of central lesions, overwhelming sepsis), the use of moderate amounts of suitable vaso-pressor agents may be rational. Such patients are considerably more susceptible to blood loss than are persons with intact and functional vascular innervation. Also direct myocardial depression as in barbiturate poisoning may be assisted by sympathomimetic agents because of their direct cardiac actions. In most of these cases while probably not required for the prevention of irreversible shock, or as a life saving procedure, unless the hypotension is really profound, the restoration of normal blood pressure leads to a subjective improvement. The patient is more alert and feels more comfortable and treatment may prevent the nausea, malaise or impairment of consciousness which often accompanies hypotension. Similar immediate effects may be seen upon the administration of such agents to patients in shock with reduced blood volume, but here the crucial question is: What is the effect on survival? This question can only be adequately answered on the basis of carefully controlled clinical investigations, where individuals with comparable degrees of shock are compared. There are many clinical reports on the use of sympathomimetic agents in patients with shock. Some of these present apparently dramatic results. A recent report describes a patient with a case of perforated ulcer, in a profound state of shock with classical symptoms, who failed to respond to fluid replacement but responded beautifully to nor-epinephrine infusion. The nor-epinephrine had to be continued for over twenty-four hours before the blood pressure became self-supporting. Its use permitted an operation which otherwise would have been considered to be out of the question. However, this represents a single case. Single cases are never very impressive to a person familiar with the vagaries of biological material and the principles of statistical validity of data.

Unfortunately, all of the clinical reports thus far available consist entirely of small series of cases in which the system of controls leaves much to be desired. None that I know of involve any very sizeable group of comparable cases in which treated patients were alternated with controls. In controlled animal experiments, there is no evidence that mortality is reduced in traumatic or haemorrhagic shock as a result of the administration of sympathomimetic amines. In a recent review, Frank cites unpublished data showing that nor-epinephrine does not prolong survival in experimental haemorrhagic shock, and does not improve hepatic blood flow during shock.

Many of these same considerations apply to several recent reports advocating

the use of sympathomimetic amines in the treatment of shock associated with myocardial infarction. The use of nor-epinephrine in this condition may seem paradoxical but it should be kept in mind that (1) all sympathomimetic agents increase coronary flow, (2) nor-epinephrine causes relatively little increase in cardiac irritability in animals with intact reflexes. The cause and nature of the shock which develops in myocardial infarction is still the subject of controversy. Some investigators claim that fluid loss occurs. Others deny this and claim that cardiac incompetence is primary. Others state that reflex vaso-dilatation is responsible. At any rate true shock in the presence of infarction is a very grave condition. It is not surprising that several of the reports of the use of sympathomimetic amines stress the production of successful pressor responses, but play down the relatively meagre survival value of the treatment. In all these reports, the treated cases are compared with general statistics rather than with control cases whose comparability is determined. The pooled data from several such reports suggest survival of as many as 30 to 40 per cent of patients presenting this syndrome treated with nor-epinephrine as compared with about 20 per cent in other types of therapy. For a difference in mortality of this magnitude, the number of cases as yet is rather small for any far-reaching conclusions. Incidentally, one group of workers employed mephenteramine (Wyamine) rather than nor-epinephrine. This and several other agents such as Neosynephrine possess properties which are very similar to nor-epinephrine. They differ primarily in requiring larger doses, having a longer duration of action, but developing tachyphylaxis (that is becoming relatively less effective with repeated or prolonged use).

The dramatic results seen in some instances suggest that in certain cases at least shock due to myocardial incompetence or reflex vaso-dilatation may be sufficiently profound to represent an acute threat to life, and that the actions of nor-epinephrine may aid in tiding the patient over this crisis.

In a recent discussion of this general problem, Dr. Mark Nickerson, an outstanding authority in the field of the pharmacology of the sympathetic nervous system, summed up his impression as follows: "I have been unable to find in the literature any report of controlled experiments in which any pressor agent administered in any dosage schedule in any type of shock, has improved the survival rate. I am forced to conclude that the available evidence fails to demonstrate any beneficial effect of vaso-constriction in protection against the development of irreversible shock."

This statement is debunking of a high order, and stresses the critical approach which the medical scientist must maintain toward new therapeutic claims. It points out that the case for these agents in the treatment of shock where reflex vaso-constriction is already present has not been proved. It does not disprove these claims, or preclude the possibility that further experiments and properly controlled clinical investigations will ultimately justify some of the hopes now placed in them. Some of the isolated clinical reports have been very suggestive. Nor-epinephrine has been studied far less extensively than epinephrine. The differences in action between these two drugs could conceivably provide a basis for some hope that nor-epinephrine may offer rational treatment in early shock

due to fluid loss. For instance, nor-epinephrine is far less toxic than epinephrine, and much larger amounts are required to produce experimentally irreversible shock. Lands, who is associated with the company which produces nor-epinephrine, has suggested that whereas epinephrine dilates the extensive vascular bed of skeletal muscle and therefore diverts large amounts of blood to this relatively unimportant bed, it may further compromise flow to vital organs. The release of epinephrine from the adrenal medulla is an integral part of the sympatho-adrenal discharge which is set up by compensatory reflexes. Conceivably, the restoration of blood pressure by nor-epinephrine might relieve the drive to this discharge and therefore reduce epinephrine release. Further, by closing down skeletal muscle vessels as well, the vital visceral organs may be placed in a better position to compete for a larger share of the available cardiac output. As yet we know very little of the effects of nor-epinephrine on specific vital vascular beds (such as the liver). These points remain to be decided by future studies, both experimental and clinical, before the degree of confidence which can be placed in this type of therapy will be apparent. We do not know whether nor-epinephrine can be of assistance in overcoming shock when the "irreversible" stage has been reached, or whether any beneficial actions which it can be expected to exert will be useful only if applied early in the condition before irreversibility develops. We cannot as yet be sure that such therapy may not actually be harmful rather than beneficial to some patients. I would suggest therefore that its use be reserved for clinical investigation or for patients who are in profound shock, who fail to respond to extensive fluid replacement or other therapeutic procedures, and whose prognosis is therefore very grave under any circumstances.

Summary

1. The salient features of the various conditions grouped under the heading of "shock" have been briefly considered. Broadly speaking, the principal feature which these conditions share in common is a persistent hypotension the proximate cause of which may be either cardiac or peripheral.

2. The action of the sympathomimetic amines on the cardiac and peripheral vascular mechanisms has been discussed, with particular reference to epinephrine and nor-epinephrine.

3. On the basis of the present experimental evidence we cannot as yet be sure that the use of sympathomimetic amines in the treatment of shock may not be actually harmful rather than beneficial to some patients. It is suggested, therefore, that its use be reserved for clinical investigation, or for patients who are in profound shock, who fail to respond to extensive fluid replacement or other therapeutic procedures, and whose prognosis therefore is very grave under any circumstances.

Résumé

Toute discussion au sujet du traitement par l'emploi de drogues doit nécessairement reposer sur deux questions—1) Quelle est la nature du délabrement à traiter? et 2) Jusqu'à quel point peut-on atteindre les buts médicamenteux par

l'emploi des outils disponibles de pharmacologie? Ces principes peuvent sembler évidents en soi et cependant l'étendue de notre ignorance sur ces deux questions nous oblige souvent à nous reposer, pour le traitement, sur des principes plutôt empiriques que rationnels. Pendant les cinq dernières années on a constaté un nombre de progrès importants dans la pharmacologie du système grand sympathique avec l'introduction d'agents dont le rôle reste encore à être complètement vérifié.

Parmi les agents sympathomimétiques la nor-épinéphrine a sans doute attiré plus d'attention que tout autre. L'intérêt renouvelé pour ce composé suit la découverte qu'il est fabriqué dans le corps et qu'il est le principal médiateur de l'activité du système sympathique, comprenant 80% ou plus de la substance libérée par l'excitation du système sympathique, le reste étant l'épinéphrine. Ces deux substances sont aussi présentes dans la sécrétion de la médullo-surrénale, mais leurs proportions relatives sont inversées.

L'action de l'épinéphrine sur les vaisseaux périphériques est complexe. Quoique les vaisseaux de la peau et de la loge splanchnique soient très resserrés, cette action est compensée par la dilatation des vaisseaux des muscles squelettiques, de sorte que la résistance totale périphérique est relativement inchangée. Par conséquent les actions excitatrices cardiaques sont principalement responsables de la réponse-hypertenseur lorsque l'épinéphrine est administrée.

L'action vaso-constrictive de la nor-épinéphrine est plus uniforme. Ses actions vaso-dilatatrices sont secondaires et son effet d'ensemble est principalement vaso-constricteur, avec une augmentation de la résistance périphérique totale. Son action excitatrice cardiaque est mitigée en grande partie chez les patients intacts par des réflexes provenant des presso-récepteurs, ce qui mène à une bradycardie par raisons des efférents vagues au coeur.

Une évaluation de l'efficacité possible des agents sympathomimétiques dans le traitement du choc exige un examen des aspects saillants des états groupés sous le titre choc. L'aspect important caractérisant tous ces états est une hypotension persistante, dont la cause immédiate peut être périphérique ou cardiaque. La méthode raisonnable et évidente dans ce cas est de songer à des moyens d'augmenter la pression artérielle. L'emploi de drogues vaso-constrictrices s'offre comme moyen commode d'aboutir à cette fin. Mais la pression artérielle est-elle une mesure sûre de la sufficance circulatoire? La responsabilité cruciale de la circulation est de fournir l'oxygène et la nourriture aux tissus. Son habileté à accomplir cette tâche dépend du *taux du flux* sanguin à travers la circulation périphérique qui est une fonction non seulement de la pression mais aussi de la résistance périphérique offerte par les petits vaisseaux sanguins. L'hypotension produite par la dilatation périphérique peut bien être tolérée parce que la résistance périphérique est basse et le flux sanguin est bien maintenu. Contrairement à cette situation le choc peut provenir d'une réduction prononcée du volume de sang en circulation causant un faible retour veineux, un faible chargement cardiaque et une diminution du débit du coeur. Dans ce cas la vaso-constriction compensatrice est assez forte et la pression artérielle est souvent maintenue à des niveaux assez normaux tandis que le taux du flux sanguin à travers les tissus est réduit. Si dans ces cas des pressions artérielles aussi basses que 30–40 mm Hg

persistent, le choc devient irréversible. Ce n'est pas la basse pression artérielle qui rend le choc irréversible mais la réduction du taux du flux sanguin à travers les organes vitaux.

Ces faits nous obligent à reconnaître que le but raisonnable du traitement de l'hypotension ou choc est le maintien d'un flux sanguin suffisant pour conserver la vitalité des organes vitaux. Quoique ce but exige une tête de pression minimale, le niveau manifestement n'est pas élevé. Dans le cas d'hypotension simple, l'effort requis du coeur décroît plus rapidement que l'écoulement sanguin. Une vaso-constriction excessive, même en présence d'un débit cardiaque normal ou élevé peut amener un choc irréversible. Comme on sait des facteurs tels la douleur, le froid, de fortes émotions et l'asphyxie qui tendent tous à produire une vaso-constriction réflexe, tendent aussi à amener le choc d'une condition d'hémoragie ou de trauma.

Toutes ces considérations mettent les savants médicaux prudents sur leur garde concernant les affirmations que les amines sympathomimétiques ont des effets salutaires dans le traitement du choc. Nous ne pouvons pas encore être sûrs qu'un tel traitement n'est pas en fait nuisible plutôt que salutaire pour certains patients. Je propose donc que son emploi soit restreint à des essais de clinique ou à des patients subissant un choc profond qui ne répondent pas à un remplacement hydrique prolongé ou autres traitements et dont le pronostic en tout cas est par conséquent très grave.

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WHY USE SPINAL ANAESTHESIA IN OBSTETRICS?*

DOUGLAS BEST, M.D.**

THE question of the use of Spinal Anaesthesia in obstetrics may be approached from two points of view, there being anaesthetists who feel that one should never use spinal anaesthesia, and others who would use it at every possible opportunity.

Let us first consider the question, "Why should one ever use spinal anaesthesia in obstetrics?" A recent writer (1) has declared that a certain number of healthy young women are doomed to death because of the continuing use of spinal anaesthesia in obstetrics. Another (2) cites the horrible complications which have occurred after subarachnoid injections for anaesthesia. I wish to state most emphatically that one should never employ a spinal technique unless one is prepared to observe the most exacting rules for its proper use. Such rules have been reiterated many times (3, 4), the most important to our minds being the autoclaving of all solutions and the use of dilute preparations of the drugs. These precautions, with meticulous surgical technique, round out a safe method. Undoubtedly when one is unable to make a lumbar tap quickly and easily in any particular case (and preferably with a No. 22 gauge needle or finer), the spinal technique should not be employed. Repeated jabbing serves only to traumatize the back, tends to cause post-spinal backache, and serves to discredit the method. Further, one should never employ spinal anaesthesia over the clear-cut objection of the patient, though many may be more concerned about the needle than about the spinal anaesthetic. Of course one must not overlook the usual absolute contra-indications to the use of spinal anaesthesia. In obstetrics the presence of placenta praevia requires special consideration, and spinal anaesthesia is often contra-indicated.

We would recommend to those who oppose spinal anaesthesia in obstetrics and elsewhere on the basis of complications which have occurred that they look to their technique before condemning an excellent form of anaesthesia. The many good anaesthetists who continue to use this method despite the clamour attest to its safety when used properly.

In the city of Hamilton we have specialist obstetricians and a gradually increasing number of general practitioners who demand spinal anaesthesia in every possible case. We ourselves tend to favour this method for the following reasons:

1. It is the anaesthetic of choice for the parturient woman with a full stomach.
2. It is the anaesthetic of choice for the heavily sedated patient.
3. It is the anaesthetic of choice to control labour and delivery while awaiting the delayed obstetrician.
4. It is the anaesthetic of choice in premature deliveries because of the maximal perineal relaxation with no foetal depression.
5. It is the anaesthetic of choice in the gravid cardiac patient.

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6. It is the anaesthetic of preference for Caesarian section since it allows a leisurely operation without harm to the child.

7. It is the anaesthetic of preference in primiparae because of the excellent perineal relaxation.

8. It is the anaesthetic of preference for many women who wish to share in the experience of child birth.

9. The post-partum period is free of nausea and vomiting; post-spinal headache is only a very minor problem in our hospital.

The following facts and figures are from our experience at St. Joseph's Hospital, Hamilton. In 1953 there were 3,854 deliveries. For these, 1,796 patients had anaesthesia with gaseous agents (nitrous oxide with or without cyclopropane), 1,312 had ether, 90 had spinals administered by non-specialist anaesthetists. The remainder had spinal anaesthesia administered by the anaesthetic staff of the hospital. The incidence of true spinal headache was low—about 5 per cent, and a severe headache occurred only once or twice during the year.

To establish the incidence of headache for the first months of this year we have gathered data for all cases, without attempting to sort out causes. There were 839 deliveries: 383 patients received gas, and 23 complained of headache once or twice; 216 had ether with two headaches reported; 201 had spinal anaesthesia and 13 complained of headache on two or more occasions, while 14 others had transient one-day headaches. Most were relieved by A.P.C. & C. tablets, with caffeine sodium benzoate being of additional help to those with the more persistent types. Only one was of some severity.

We feel that a few points of technique should be emphasized. The most important single point is the very low dosage requirement. We use two or three mg. of pontocaine made up with 1 per cent procaine and glucose in the following manner: we mix 2 cc. of 2 per cent pontocaine with 2 cc. of 10 per cent glucose, discard one-half or three-quarters of this mixture, then draw up to 8 or 9 cc. of 1 per cent procaine into the syringe to a total volume of 10 cc. Of this mixture a dose is given to correspond with the pontocaine content, not to exceed 3 mg. The injection should take a full minute, and must not be made during a uterine contraction or the level of anaesthesia may go to the clavicles. The expected level of anaesthesia is about the tenth thoracic segment—that is, this is not a saddle block. The dosage is low and the spinal anaesthetic level is medium low. A pillow under the shoulders, with or without slight Trendelenburg tilt, will keep the anaesthetic level about the umbilicus.

Comment

We all know that no anaesthetic method is perfect in all cases. In obstetrics many women wish to be asleep, while others want to be awake. One should adapt one's technique to the patient's desires, within the limits of good anaesthetic judgement. We favour subarachnoid block for simplicity; for the quiet course of anaesthesia, delivery, and the post-partum period; for the ideal relationship to the baby; for the relaxation of the perineum; and to allow those who desire it to watch the birth of their baby. We use more of the gaseous agents than of spinals simply because the doctor or the patient wishes it for personal reasons, or

because there is not sufficient time to administer the subarachnoid block. By and large the results are good either way.

In conclusion one should simply say that the method best suited to the patient is the anaesthetic of choice in obstetrics. Whether it be gas, ether, trilene, pudendal block, or any combination which is to be employed, the best interests of the two lives involved are paramount.

RÉSUMÉ

On se sert de l'anesthésie lombaire en obstétrique depuis bien des années à l'hôpital St. Joseph de Hamilton. Les résultats ont été satisfaisants. Les bons résultats dépendent d'une technique méticuleuse, d'un dosage faible de la drogue, de l'emploi de solutions diluées des drogues et du choix approprié des malades. Les séquelles post-lombaires se sont bornées à des maux de tête dans environ 5% des malades, et à des douleurs dans le dos. Il n'y a pas en de symptômes neurologiques. La technique est recommandée mais on devra observer la méthode la plus exacte de procéder.

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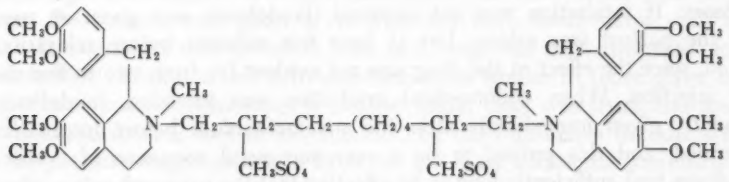
THE CLINICAL USE OF LAUDOLISSIN*

SHIRLEY A. FLEMING, B.A., M.D., F.F.A.R.C.S.**

RELAXANT drugs were introduced into clinical anaesthesia twelve years ago. Since that time numerous preparations of this type have been produced for investigation and use by anaesthetists. Some of these have remained as useful additions to the pharmacopoeia, others have not proved acceptable to the practising clinical anaesthetists. Each one has had to be shown to have some characteristic the possession of which makes the use of it under some circumstances more desirable than d-tubocurarine, the relaxant to which all others have been compared.

Laudolissin is a relaxant drug, its particularly attractive qualities being that it is synthetic and that it acts for a considerably longer period than d-tubocurarine.

Our experience with laudolissin has been clinical, but a brief review of the laboratory and clinical findings of other investigators which served as a background to its use will be of interest. The pharmacological activity of laudolissin, also known as Allen and Hanburys' Compound 20, has been studied by Collier, Macauley, Bodman and Taylor who synthesized it (1, 2, 3, 4, 5). Laudolissin is a decamethonium compound with modified isoquinolone groupings at each end of the chain:



Decamethylene bis-[1:2:3:4-tetra hydro-6:7-dimethoxy-1-(3':4'-dimethoxybenzyl) -2-methylisoquinolinium] dimethosulphate.

The investigations in the laboratory were made on both animals and conscious human volunteers.

1. Laudolissin acted as a curarizing agent, the muscle itself being excitable by direct stimulation while the animal was under a paralyzing dose of the drug.
2. Voluntary muscle was paralyzed without initial stimulation.
3. Neostigmine antagonized laudolissin.
4. The potency of laudolissin in man was one-half that of d-tubocurarine; it was more potent in the rabbit and cat but less so in the mouse and rat.
5. An equipotent dose of laudolissin acted longer than d-tubocurarine, while doses given less than an hour apart might have an accumulative effect.

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6. Small doses of suxamethonium hastened recovery from laudolissin; larger doses caused paralysis followed by more rapid recovery.

7. There was little difference from d-tubocurarine as regards histamine release; if anything, less histamine was released by laudolissin.

8. In animals laudolissin has one-quarter the ganglion blocking effect of d-tubocurarine.

9. Ether acted synergistically; thiopentone had no effect on the toxicity of the drug.

In 1952, Bodman, Morton and Wylie (4) reported a series of 186 surgical cases in which laudolissin had been used. In 1953, Binning(6) reported its use for 100 cases. Our series includes 103 patients.

Laudolissin is dispensed in 1½ cc. ampoules containing 30 mg. of the drug, that is 20 mg. in each cc. As 2 mg. of laudolissin have about the same potency as 1 mg. of d-tubocurarine, for many patients the initial dose of laudolissin was 30 mg., that is, the entire contents of the ampoule. For additional doses it was found useful to dilute the 1½ cc. to 5 cc., thus having 6 mg. of the drug per cc. When laudolissin was given through a needle immediately after thiopentone a heavy, white precipitate formed which on one or two occasions stopped up the needle. With an intravenous running this could not occur. Usually, because of the surgical procedure proposed, the patient required an intravenous infusion which made the administration of the drug easier. The usual sequence of events during induction of the anaesthetic was the administration of thiopentone followed by the maintenance agent of choice and suxamethonium if intubation was considered necessary. If intubation was not required, laudolissin was given at any time after the patient was asleep, but at least five minutes before relaxation was desired, since the effect of the drug was not evident for from two to five minutes after injection. When endotracheal intubation was intended, laudolissin was frequently given immediately after the suxamethonium before intubation was performed, and this proved to be a very successful sequence of events. The laudolissin took sufficiently long to be effective that the suxamethonium effect was over before it was active and neither drug interfered with the benefit of the other.

The only criterion for the use of the drug in these cases was that the operation was expected to last about one hour or longer, although in thirteen instances this did not happen. No other unusual drug was used for the 103 patients in this group. There were 56 females and 47 males, the ages ranging from 13 to 73 years. Seventy-four operations were intra-abdominal, 35 lower and 39 upper; 18 were orthopaedic or neurosurgical major procedures; the remaining patients included some who did not require relaxation but with whom it seemed interesting to use the laudolissin to note its effect in producing a quiet anaesthetic with less than the usual amount of sedative anaesthetic agent over a long period. The pre-operative sedative for the majority of the patients was a combination of morphine and hyoscine.

Thiopentone was used for induction of anaesthesia in all but two cases when the operation was Caesarian section; here cyclopropane was used throughout. In 57 cases cyclopropane was used for maintenance, in 24 thiopentone was continued with nitrous oxide, in 18 thiopentone, nitrous oxide and trilene were

used, and for 4, ether. Forty-three of the patients were intubated using suxamethonium. It was, of course, quite adequate to wait for the optimum relaxation of laudolissin to intubate, 5 patients being done in this way. One man had had an initial 30 mg. of laudolissin followed an hour later by 6 mg. One-half hour after this the cuff of the endotracheal tube broke and reintubation was necessary. The damaged tube was withdrawn and another tube inserted with neither difficulty nor reaction. In the majority of the patients a topical spray was used before intubation. The onset of relaxation due to laudolissin seemed to vary from about two to five minutes, occasionally accompanied by marked respiratory depression, but more often not, and it was only when the abdomen was opened with great ease that the degree of relaxation was apparent, for the respiratory depression usually seemed much less than would have been expected with an equally relaxing amount of d-tubocurarine.

At no time was the surgeon aware that a new relaxant drug was in use, and during eight operations the surgeon commented on the extraordinary relaxation. Only anaesthetists know how difficult it is to refrain from asking about the degree of relaxation, and how readily they are apprised of any deficiency in that respect, so these favourable, unsolicited remarks were much appreciated. In three instances the anaesthetist felt that the operating conditions were only fair, although there were no complaints. One of them was the first case in which the drug was used, and probably the initial dose was not large enough, although intubation had been performed without difficulty under laudolissin. One of the other patients required a deeper anaesthetic, the other satisfied the surgeon but from the anaesthetist's point of view would have been better with more relaxant. It was found that an initial dose of 30 mg. was most successful for an intra-abdominal operation, and provided conditions similar to those given by 15 mg. of d-tubocurarine. Sometimes a smaller initial dose was used, the amount being determined, as is that of any relaxant, by the impression the anaesthetist has of the patient's requirements. In 21 of the 103 cases additional laudolissin was given in the first hour; several of these had had small initial doses, others were having controlled respiration. The maximum amount given was 70 mg., for operations lasting two and one-half and three hours. In several instances only 10 mg. were given when relaxation was not the reason for the use of the drug.

Fifteen patients were seen to require more relaxation for closure of the peritoneum. This was accomplished in several ways to determine the effects produced by various substances on the patient already under laudolissin. Thiopentone was given twice, ether was added three times when it had not been used in the course of the anaesthetic, suxamethonium was added eight times, and laudolissin added twice, all successfully. When ether was added, a few breaths sufficed. On 18 occasions atropine and prostigmine were given at the end of the operation because of respiratory depression, one of the instances being after an additional 10 mg. of laudolissin had been given for closure. Each time the response to the prostigmine was prompt, excellent and permanent. Tensilon was given twice with a good response.

As with other relaxant drugs, respiratory depression was variable, depending on the patient, apparently, rather than on the drug. The general impression was

that the depression was less than it would have been with doses of d-tubocurarine producing the same degree of relaxation. Twenty-seven patients had no respiratory depression. Twenty-one patients had assisted or controlled respiration almost throughout their procedure. Very few of the patients were not reacting on leaving the operating room, and these recovered reflexes shortly after reaching the recovery room. There was one death in the recovery room following a cholecystectomy; the operation had lasted 135 minutes, during which time the patient had had controlled respiration under a total of 60 mg. of laudolissin with nitrous oxide and ether endotracheal anaesthesia. She received 1/100th of a grain of atropine and 5 mg. of prostigmine ten minutes before the completion of the operation and was awake in satisfactory condition on leaving the operating room. Cardiac arrest occurred forty-five minutes after she reached the recovery room. During cardiac massage the heart ruptured at the site of an infarct. It was felt that the laudolissin had had no connection with the death.

There were no post-operative sequelae which were attributable to the use of laudolissin.

During operation, in the great majority of cases, the pulse rate remained remarkably constant, within the normal limits, and the blood pressure also remained fairly constant. Certainly neither pulse nor blood pressure seemed to be affected by the laudolissin. A seriously ill woman had had two previous operations, one recently and one two years before, during which there had been tachycardia and questionable fibrillation. Ether had been used on the second occasion because of the earlier history. It was considered unnecessary and, perhaps, unwise, to pass an endotracheal tube. Following a sleep-producing dose of thiopentone she had, for a four-hour upper abdominal procedure, 40 mg. of laudolissin with cyclopropane. Only twice during that time was her pulse over one hundred and she had intermittant pulsus alternans, for which a procaine drip was added. Her pressure varied within normal limits. This was her least eventful anaesthetic and her course was good.

Another patient had received a thiopentone, curare, demerol, nitrous oxide anaesthetic early in the day for a minor procedure, during which he was very difficult to anaesthetize. When the major procedure for which he was given a thiopentone induction followed by nitrous oxide and trilene and laudolissin was over, his respirations were still depressed. As it was eighty minutes since the laudolissin had been given, it was considered likely that the depression was due to other drugs. Coramine was therefore administered and the respiratory depression was rapidly relieved. The laudolissin had provided excellent conditions for operating on this patient.

For two neurosurgical laminectomies laudolissin was given because the patients were not settling down, and promised to require large quantities of anaesthetic agents. They responded immediately and were carried easily for the duration of the operation without respiratory depression.

For the Caesarian sections, 15 mg. of laudolissin were used with no demonstrable effect on the babies.

From our clinical experiences laudolissin has proved itself a useful drug. When the supply was finished we missed it. There are many operations for which

a longer-acting relaxant than d-tubocurarine is very convenient. We had no electrocardiograms taken during operations, but in three recorded in one of the other clinical series no changes were noted. As with other investigators, we found no evidence of bronchoconstriction, nor was there evidence of haemolysis, thrombosis or phlebitis. We are inclined to agree with them, also, that the antagonistic effect of suxamethonium was not as evident clinically as it was reported to be in animals.

One of our anaesthetists has used laudolissin as the relaxant for eighteen additional patients who received largactil during their surgical procedure. These patients were not included in the above series. There was an impression that largactil potentiates the effect of laudolissin as it has been said to do in the case of other relaxants.

In conclusion it may be said that laudolissin was found a good relaxant of the curare type, lasting much longer than d-tubocurarine and, therefore, being more convenient to use for operations requiring relaxation for an hour or longer. No undesirable side effects were experienced. The fact that it is synthetic means that it should be cheaper and that the supply is not likely to fail.

Dr. R. A. Gordon, Dr. I. M. MacKay and Dr. S. L. Vandewater are to be thanked for undertaking to use laudolissin in a number of cases, and provide records of them and for their personal impressions regarding the drug.

Our thanks are due to Messrs. Allen and Hanburys Company for the supply of the laudolissin.

Summary

Laudolissin is a new synthetic relaxant drug of the curare type, with a duration of action considerably longer than that of d-tubocurarine. In clinical use laudolissin has been found to be more convenient than d-tubocurarine for operations requiring relaxation for an hour or longer. No undesirable side effects were experienced in 103 cases in which the drug was used.

Résumé

La laudolissine est un relâcheur synthétique dont l'efficacité est de plus longue durée que celle de la d-tubocurarine. C'est un composé du décamethonium avec groupements isoquinolones modifiés à chaque bout de la chaîne. La laudolissine agit comme agent curarisant, causant une paralysie du muscle volontaire sans excitation initiale; elle est neutralisée par la néostigmine. Chez l'homme 2 mgm de laudolissine sont aussi puissants que 1 mgm de d-tubocurarine. Des dosages administrés à des intervalles de moins d'une heure peuvent s'accumuler. L'éther a un effet synergique. La laudolissine diffère peu de la d-tubocurarine quant à la libération d'histamine.

La laudolissine s'obtient en ampoules de 1½ cc contenant 30 mgm de la drogue. Un lourd précipité blanc se forme avec le thiopentone. Il faut de deux à cinq minutes pour que la drogue produise le relâchement. On s'est souvent servi du suxaméthonium pour permettre plus tôt l'intubation. L'action de la laudolissine n'était pas changée. On pouvait l'administrer immédiatement après le suxaméthonium mais avant l'intubation.

Les 103 patients de cette série étaient âgés de 13 à 73 ans; 74 subissaient des opérations abdominales, 18 des opérations majeures orthopédiques ou neurochirurgicales, les autres une variété de procédés dans lesquels la laudolissine servait à diminuer la quantité de l'agent anesthésique nécessaire. Vingt et un de ces patients reçurent une quantité additionnelle de laudolissine pendant la première heure. Pour obtenir un relâchement plus profond pour l'occlusion, des quantités additionnelles de laudolissine, d'éther, de thiopentone et de suxaméthonium ont prouvé leur efficacité. Vingt-sept des patients ne témoignèrent aucune dépression respiratoire.

Il y eut une mort dans la série avec laquelle la laudolissine ne semblait pas associée. L'emploi de la laudolissine ne semblait influencer ni le pouls ni la pression artérielle. Aucuns effets secondaires ne se déclarèrent.

Dans les expériences cliniques la laudolissine s'est trouvé être un bon relâcheur du type curare, à durée beaucoup plus longue que la d-tubocurarine et par conséquent plus commode à employer dans les opérations exigeant un relâchement d'une heure ou plus.

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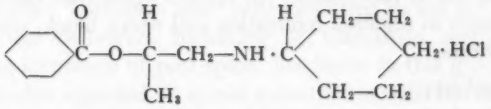
CLINICAL EXPERIENCE WITH HEXYLCAINE HYDROCHLORIDE (CYCLAINE)*

R. A. Gordon, *C.D.*, B.Sc., M.D., F.R.C.P.(C), F.F.A.R.C.S., D.A., F.A.C.A.**

In spite of the large number of effective local anaesthetic drugs already available on the market, the search continues for drugs of greater potency and more prolonged action, with low toxicity and absence of tissue irritation. One of the latest substances to be presented for use as a local anaesthetic is Hexylcaine (Cyclaine).

Hexylcaine is 1-cyclohexylamino-2-propylbenzoate hydrochloride, and the structural formula is



This substance was synthesized by Hancock and Cope, and described in 1944 (1). Evaluation as a local anaesthetic substance was done by Kuna and Seeler (2).

Physical Properties

Hexylcaine has a molecular weight of 297.85. It is freely soluble in water to a concentration of 12 per cent, and is not altered by ordinary sterilizing procedures. The pH of a 1 per cent solution is 4.4, as compared with pH 6.0 for freshly prepared solutions of procaine, HCl.

Toxicity

The toxicity of Hexylcaine was investigated in laboratory animals by Beyer *et al.* (3), and compared with Procaine, Neothesin, Cocaine, Butacaine, Tetracaine, and Dibucaine. The intravenous LD_{50} was determined in mice, guinea pigs and rabbits, and on this basis the absolute toxicity appears to be about ¾ that of cocaine, ⅛ that of Dibucaine (Nupercaine), and three times that of procaine. The subcutaneous LD_{50} in guinea pigs when the drug was dissolved in 1/50,000 epinephrine solution was 385 mg/kg as compared with 87 mg/kg for cocaine, 78 mg/kg for tetracaine (Pontocaine) and 500 mg/kg for procaine.

Activity

The activity of Hexylcaine was likewise investigated in laboratory animals by Beyer *et al.* (3). The activity was tested on the intact sciatic nerve of the guinea pig, and the AC_{100} for Hexylcaine was found to be ¼ of 1 per cent as compared to 1 per cent for procaine, ½ of 1 per cent for cocaine and ⅛ of 1 per cent for dibucaine. This drug is, therefore, four times as potent as procaine, twice as potent as cocaine, and half the potency of dibucaine. It was found, moreover,

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that any concentration of Hexylcaine which produced anaesthesia gave longer anaesthesia than that produced by 2 per cent procaine HCl.

Relative Toxicity

Relating the toxicity figures to those for activity it is found that Hexylcaine has a therapeutic ratio more favourable than that of procaine (584 compared to 353 for procaine).

Spinal toxicity studies in animals have shown that the MLC for Hexylcaine is four times the active concentration (3). Activity studies with spinal anaesthesia in dogs gave a duration of anaesthesia roughly twice that with procaine.

Clinical Application

A number of reports have appeared in the literature recording most favourable data on the clinical use of Hexylcaine. All reports agree that this is a satisfactory agent for employment in regional infiltration and nerve block, spinal anaesthesia, and topical anaesthesia.

1. *Regional Anaesthesia*

The use of Hexylcaine in regional block anaesthesia has been reported by Hudon (4), Orkin and Rovenstine (5), and Crawford (6). These reports have been marked by unanimity with respect to the potency and usefulness of the drug, and the low incidence of toxic reactions in clinical use.

Personal experience with this drug began in March, 1952, when I commenced to intersperse therapeutic blocks done with Cyclaine amongst those done with procaine and metycaine, which I had been using for some years. The drug proved to be a most satisfactory local anaesthetic agent. Two factors stood out in comparison with the other two drugs mentioned: (1) the rapid onset and wider diffusion of the Cyclaine solution, and (2) a somewhat greater degree of tissue irritation, made evident by some persistent tenderness at the site of injection, which lasted sometimes for several days. The more rapid onset of a complete block was a decided advantage, and the tissue irritation was not so great as to be a real inconvenience to the patient. During the past year I have employed Cyclaine exclusively in my private practice, and since May of 1953 exclusively in those blocks which I personally have done about the hospital. All blocks have been done with the 1 per cent solution prepared by Sharpe & Dohme, Inc. The drug has proved uniformly satisfactory in the production of anaesthesia. The following regional anaesthetic procedures have been recorded:

Procedure	*Average amount used*	*Number*
Stellate ganglion block	15 cc.	68
Lumbar sympathetic block	20 cc.	41
Brachial plexus block	30–40 cc.	18
Caudal blocks	25 cc.	4
Other blocks (pudendal, sciatic, femoral, popliteal, ulnar, median, transverse scapular, vagal)	3–30 cc.	37
Total blocks with Cyclaine 1 per cent		168

No patient in this series has suffered a serious toxic reaction. Four patients only have complained of palpitations, or of feeling faint.

The only block which might be classed as a failure was a partial brachial plexus block, due to technical error, which was still adequate for the reduction of a Colles' fracture. In nearly every case the onset of complete anaesthesia or evidence of sympathetic block has been much more rapid than might have been expected following the use of procaine in a similar situation. We have had brachial plexus blocks which lasted more than four hours, and the caudal blocks have persisted for periods from 4½ to 5 hours. There have been no local complications at the site of injection.

2. *Spinal Anaesthesia*

Ruben and Anderson (7) in 1949 reported a series of 500 spinal anaesthetics done with Hexylcaine. Torkelson and Cooley reported its use for spinal anaesthesia in 1,000 obstetrical deliveries, including 25 Caesarean sections. These latter authors report an incidence of post-spinal headache in this group of 3.6 per cent (36 patients). Hudon reported 64 spinal anaesthetics with the drug.

Up to the present time we have used the drug thirteen times in spinal anaesthesia. Nine of these patients underwent Caesarean section, three transurethral resection of the prostate, and one reduction of a fractured femur. The drug has been used in a hyperbaric preparation containing 25 mg. per cc. of the drug in 10 per cent glucose solution. For Caesarean sections 30 mg. has been used, expanded to 2 or 3 cc. with spinal fluid before injection, and well mixed. In four of the patients undergoing Caesarean section the head of the table was then lowered about 10 degrees until the anaesthesia reached the costal margin, when the table was tilted slightly in the foot-down position until the peritoneum was opened, when the table was either levelled or trendelenburged in accordance with the requirements of the surgeon. In one of these cases a vasopressor drug was given before the induction of spinal anaesthesia, and no blood pressure drop was recorded. In the others no vasopressor was given, and the blood pressure declined about 10 mm. Hg on the average. In these four patients the anaesthesia outlasted the operation. In the fifth case for Caesarean section the head of the table was not lowered after the injection and anaesthesia to the costal margin resulted. However, anaesthesia became inadequate after 55 minutes and supplementation was required. I am inclined to believe that in this case the concentration of the solution at the upper levels was inadequate.

The patients who have had spinal anaesthesia with Hexylcaine for transurethral resection of the prostate have, with one exception, received a dose of 25 mg. in 1 cc. of glucose 10 per cent expanded to 2 cc. The foot of the table has then been lowered, concentrating the anaesthesia in the sacral region. One patient received 50 mg. expanded to 4 cc., and anaesthesia extended to the upper thorax.

From our present small experience, I would conclude that Hexylcaine is a very satisfactory drug for use in spinal anaesthesia.

3. *Topical Anaesthesia*

Published reports by Orkin and Rovenstine (5), Ray and Vinson (8), Hudon

and Jacques (4), Arcuri, Newman and Burstein (9) record the excellence of this drug as a topical anaesthetic agent. Burstein demonstrated that topical anaesthesia with 5 per cent Cyclaine spray prevented electrocardiographic changes in much the same proportion of patients as did the administration of procaine and its derivatives, but further that in some cases the drug actually reversed arrhythmias produced by anaesthesia.

I have personally used the drug in sixty cases for the introduction of an endotracheal tube under pentothal anaesthesia alone, and have found uniformly that if the larynx and trachea are adequately sprayed with 5 per cent solution of Cyclaine, using 2 to 4 cc., that an endotracheal tube may be inserted with no reaction of any kind from the patient in three to five minutes. I have employed the drug successfully on one occasion to relieve laryngeal spasm following laryngoscopy. The drug has also been employed for introduction of an endotracheal tube by other members of the staff in many cases, and found to be satisfactory. It has been used for topical anaesthesia for bronchograms with complete satisfaction and on the otolaryngology service for bronchoscopic examinations. There has been no evidence of a toxic reaction of any kind in these patients.

Summary

From our experience Hexylcaine would appear to be a useful local anaesthetic agent having the advantages of low relative toxicity, prolonged and rapid action, and excellent topical anaesthetic properties.

Résumé

Malgré le grand nombre de drogues anesthésiques locales efficaces déjà disponibles sur le marché, l'on continue de rechercher des drogues plus puissantes, à action plus prolongée, à faible toxicité et absence d'irritation du tissu. Une des substances les plus récentes qui s'offre comme anesthésie locale est l'Hexylcaïne (Cyclaïne). La Cyclaïne est quatre fois aussi puissante que la Procaïne et trois fois aussi toxique dans des expériences de laboratoire, donnant un rapport médicamenteux plus favorable que celui de la Procaïne. L'auteur s'est servi de la Cyclaïne en solution de 1% pour l'anesthésie régionale dans 168 cas, en dosages allant jusqu'à 30 mg pour l'anesthésie lombaire et en solution de 5% pour l'anesthésie topique du larynx et de la trachée avant l'intubation endotrachéale dans 54 cas avec des résultats tout à fait satisfaisants. Aucunes réactions toxiques majeures ne se sont déclarées et les troubles cardio-vasculaires secondaires ont été rares. L'anesthésie régionale a duré jusqu'à cinq heures et l'anesthésie lombaire environ une heure et demie. La "Cyclaïne" semble être un agent anesthésique local utile, à toxicité relativement faible, à action prolongée et rapide et possédant d'excellentes propriétés anesthésiques topiques.

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PROPHYLAXIS AND TREATMENT OF CARDIAC ARREST*

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COMPLETE and successful resuscitation from clinical death implies that adequate measures must be instituted during the interval of time which extends from cardiac arrest up to the moment which precedes the initial irreversible biological destruction of the cerebral tissues. This interval of time has been established experimentally by Weinberger, Gibbon and Gibbon (1) at three and one-half minutes. Clinically, it is generally agreed that this interval may extend to four minutes (2).

The most important factor which will influence the viability of tissues following cardiac arrest is the degree of oxygen reserve in the tissues at the time of the arrest. If through negligence or uncontrollable circumstances resuscitative measures are instituted after the four-minute time limit, the situation is still not hopeless provided the patient was well oxygenated at the time of the arrest regardless of its cause.

CAUSES OF CARDIAC ARREST

In order to institute proper prophylactic measures and treatment, it is essential to be familiar with the common causes of sudden cardiac failure.

Since cardiac arrest may occur as a result of either surgical or anaesthetic factors, we shall consider these separately.

Cardiac Arrest of Surgical Origin

Vago-vagal reflexes have an inhibitory influence on the intrinsic conductive mechanism of the heart. This may lead to cardiac standstill when the specific tissue in the heart is depressed by anaesthesia (3). Vagal inhibitory activity may occur during intra- or extrathoracic manipulations such as rib stripping and retraction, pleural incision, traction and clamping of pulmonary hilar structures, dissection of pulmonary artery or aorta and direct vagal stimulation. Abdominal visceral and mesenteric traction, and irritation of a hypersensitive carotid sinus may also lead to asystole through the same mechanism. Concomitant hypoxia greatly lowers the resistance of the heart against these inhibitory reflexes (4).

Mechanical compression of the heart and great vessels during direct manipulation or by retractors interferes with cardiac activity and is a real hazard.

Air embolism may occur when the posture of the patient favours a negative venous pressure at the site of the operation. This condition is fulfilled during neurosurgical operations performed in the sitting position or in pelvic operations with the patient subjected to a steep Trendelenburg inclination. In either situation, a medium-sized vein, left open, will allow air to be aspirated (5).

Surgical and haemorrhagic shock, if not controlled, may lead to cardiac arrest due to stagnant hypoxia.

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Cardiac Arrest due to Anaesthetic Causes

Increase in cardiac irritability by sensitization to adrenalin either of endogenous or exogenous origin may occur with cyclopropane, trichlorethelene, ethyl chloride and chloroform. If proper prophylactic measures and adequate selection of anaesthetic agents are not respected arrhythmias may occur and progress to ventricular fibrillation and arrest.

Vago-vagal and vago-sympathetic (6) reflexes are prone to occur with currently used anaesthetic procedures. When highly reflexogenic zones of the trachea and bronchi are irritated by the insertion of an endotracheal airway, by a sudden high concentration of an irritant anaesthetic agent, or by bronchial aspiration, inhibitory reflexes may occur and lead to asystole. Pentothal potentiates vagal activity and serious cardiac inhibitory reflexes may occur when it is used for certain surgical procedures on the neck.

Anaesthetic overdosage may lead to myocardial depression and arrest. Usually the condition sets in gradually and for this reason is easily diagnosed before it produces asystole.

Neurogenic spinal shock places a great strain on the heart. A high spinal anaesthesia which goes beyond the safe limit of spontaneous physiological reserve not artificially compensated may lead rapidly to myocardial ischaemia and cardiac arrest. There is widespread sympathetic paralysis involving the cardiac accelletor nerves. Combined with predominant vagal activity, this leads to stagnant hypoxia. The heart cannot withstand the added strain of anoxic hypoxia from respiratory paralysis.

Other causes of anoxia or asphyxia threaten the heart of the patient. Excessive premedication, respiratory obstruction, inadequate blood replacement, improper management of controlled or assisted respiration in deep anaesthesia or in curarized patients may all lead to cardiac ischaemia. Anoxia superimposed on a heart already depressed by anaesthetic agents decreases the capacity of the specific tissue to form stimuli. Under such conditions the heart becomes vulnerable to vago-vagal reflexes (3). In cardiac arrest associated with hypoxia the prognosis is very severe. Irreversible damage to the brain and heart may have occured even before resuscitative measures are instituted.

Intolerance to local anaesthetic drugs may result in cardiac arrest either by central cardiovascular depression or by direct depression of the myocardium (7).

Prophylaxis of Cardiac Arrest

Surgical Prophylaxis

Close collaboration between surgeon and anaesthetist must exist at all times.

With regard to vago-vagal reflexes, undue traction on thoracic or abdominal viscera should be avoided. Exteriorization of organs should be performed gradually. Infiltration of hyperactive areas with procaine before manipulation will avoid serious trouble. The position of retractors should be checked often and should not interfere with cardiac activity.

If the surgeon's attempt to accomplish a technical masterpiece be detrimental to the patient, he must sacrifice quality for efficiency and expediency in his work.

In all cases of direct intervention on the heart, the surgeon should insist on

a continuous or intermittent electrocardiographic record with a responsible person in attendance capable of interpreting the results (8). The surgeon must make certain that reflex activity is sufficiently obtunded before starting the incision.

Adrenalin-soaked sponges and packs should not be used without the knowledge of the anaesthetist. Whenever necessary the anaesthetist will oblige by changing to another compatible agent.

Excessive bleeding must be avoided.

Anaesthetic Prophylaxis

Here again mutual respect, perfect understanding and close co-operation amongst members of the surgical team are prerequisites if cardiac emergencies are to be avoided during all major operations. At no time should relations between surgeon and anaesthetist be strained. The surgeon should realize that there are legitimate reasons for slow, difficult anaesthetic procedures just as there are reasons for slow, tedious surgical work. Let it be understood that the anaesthetist is working primarily for the patient. He resents order-like requests devoid of scientific reasoning. Under tense working conditions the one to falter is not always the anaesthetist. Indeed courtesy plays an important role in prophylaxis of cardiac arrest.

The most important prophylactic means of preventing cardiac emergency is adequate oxygenation. It is the anaesthetist's duty to keep the highest possible oxygen concentration in the tissues of his patient provided the surgeon will not interfere by his exigencies. So called ideal operating conditions necessitating protracted periods of apnoea or depressed breathing are a hazard to any patient and are to be deplored. For intrathoracic procedures, intermittent oxygenation is not enough and indeed the intervals of apnoea to provide adequate facilities for surgery produce periods of anoxia which have cumulative deleterious effects upon the heart muscle and specific tissue. Uninterrupted controlled or assisted respirations, so valuable to the patient, are actually an advantage to the surgeon. Regardless of lung retraction, efficient tidal air is maintained by overdistention of non-restrained pulmonary tissue. Paradoxical respiration, often fatal to patients, is suppressed, which, for the surgeon, means absence of annoying excessive diaphragmatic activity and mediastinal shifting. In present-day anaesthesia, the patient must be well "coloured" at all times so that different shades of cyanosis should never be a criteria for the degree of tolerance to anoxia (9).

Impending cardiac arrest is often preceded by predominant vagotonic effects manifested by bradycardia and lowering of blood pressure. Simultaneously, displacement of the pacemaker and appearance of ventricular premature beats may occur (8). At such a time the patient should be well oxygenated and atropine given intravenously in appropriate dosage. Reid (3) considers atropine one of the most valuable drugs to prevent cardiac arrest during the course of general anaesthesia. It blocks the interference with stimulus formation in the auricles.

For intrathoracic procedures, it has been our impression that a continuous intravenous infusion of procaine helps to protect the heart from sudden vagal inhibition. Small quantities are administered to avoid undue depression of the myocardium and of the autonomic functions of the heart. Usually not more than

one gram of 0.2 per cent solution in 5 per cent glucose is administered during the course of an intrathoracic operation on an adult patient. For some time we have been using Largactyl (chlorpromazine) instead of procaine. This drug appears to give protection to the heart; however it is too early for us to fully appraise its value in this regard, our clinical and laboratory investigations being as yet incomplete.

Diagnosis of Sudden Cardiac Failure

Role of the Anaesthetist

In extrathoracic operations rapid and early diagnosis of sudden cardiac failure is the most important responsiblity of the anaesthetist if resuscitation is to succeed and if the patient is to remain free from neurologic complications. Delay in diagnosis is the chief cause of failure. Time-consuming diagnostic procedures such as taking blood pressure or listening for heart sounds must be excluded. The following clinical signs of cardiac arrest or fibrillation require only a few seconds to ascertain and their presence should bring an immediate request to the surgeon to start resuscitation: imperceptible peripheral pulse; dilated pupils, the degree of dilatation varying with the degree of anoxia and depth of anaesthesia at the time of the arrest and elapsed time between arrest and diagnosis; ashen grey colour of the skin; pallor or cyanosis; sighing respiration or apnoea, depending on depth of anaesthesia and absence or presence of curarization. If respirations are still active at the time of arrest, ideally, diagnosis should be established before subsequent appearance of apnea.

When the site of operation favours a negative pressure in the exposed veins, sudden cardiac failure points to gas embolus unless another mechanism is plainly evident.

It must be recognized that apnea and imperceptible peripheral pulse do not imply cardiac arrest and do not necessitate extreme resuscitative manoeuvres if other signs are not present. Should spontaneous respiratory activity cease at a time when cardiac function appears to be at a standstill, the administration of pure oxygen by means of controlled respiration will not only serve as a diagnostic procedure but also as a therapeutic measure. This necessary procedure will determine the efficiency of residual cardiac activity if present and rule out cardiac arrest by maintenance of a good colour in the patient. Operative procedure should not be resumed until blood pressure is adequate as determined by the anaesthetist.

Role of the Surgeon

When the thorax is open direct visualization and palpation of the heart confirms the diagnosis.

When the abdomen is opened, verification of diagnosis is obtained by palpating the heart from below the diaphragm or the abdominal aorta.

In extrathoracic and extraabdominal operations where the surgeon is not in a position to feel the heart or a large artery, palpation of the heart through an opening in the left chest wall is the only positive diagnostic procedure. When the patient's appearance has obviously and suddenly deteriorated to a death-like

state there is no time for consultation or meditation. Stethoscopes and ophthalmoscopes will not save the patient at this stage (10).

When an electrocardiogram machine is already in operation, there is no problem as to the state of cardiac activity or inactivity. However, if fibrillation does not exist, there is no way of telling whether residual cardiac action is efficient or not. If usual remedial measures do not re-establish a palpable pulsation within a few seconds, cardiac massage must be instituted.

Treatment of Cardiac Arrest

Role of the Anaesthetist

As soon as cardiac arrest is assumed, or definitely established, all gaseous or volatile anaesthetics must be eliminated from the breathing bag and oxygen delivered to the patient. If the patient is not already intubated, artificial respiration must begin at once with the mask.

A five-degree head-down position will help irrigate the nervous centres.

A transfusion will contribute to the maintenance of an adequate peripheral circulation and will increase venous return.

Role of the Surgeon

It should not appear strange for the anaesthetist to discuss the role of the surgeon in cardiac resuscitation. There are occasions where the anaesthetist himself must perform cardiac massage.

If sudden failure of the heart to maintain circulation occurs during an intrathoracic operation, massage must be started at once.

When the abdomen is open, subdiaphragmatic or transdiaphragmaticcardiac massage may be attempted as a means of stimulating the heart into activity rather than as a means of producing efficient circulation. Thoracotomy is the method of choice.

In extrathoracic and extraabdominal operations valuable time must not be lost in preliminary attempts at resuscitation. These attempts are simple manoeuvres such as strenuous thumping and application of hot packs over the precordial region; transthoracic needle puncture of the heart to produce mechanical stimulus or to inject drugs directly into the heart chambers; indirect cardiac massage over the left hypochondrium. One, and only one of these procedures may be attempted by the surgeon with his left hand while his right hand is reaching for the knife. These procedures will not cause a heart in ventricular fibrillation to revert to a normal rhythm. Cardiac massage via thorocotomy should not be withheld as a last resort when all else has failed (11).

A rapid rate of massage seems to give a greater flow of blood and does not appear to interfere with ventricular filling (12). If necessary, the pericardium may be opened to improve massage.

To shunt more blood into the coronary and cerebral circulation, the aorta should be compressed just below the origin of the left subclavian artery during massage. It follows that great care must be taken not to obstruct the coronary vessels.

Since there is absence of adequate coronary blood flow during fibrillation,

cardiac massage must precede defibrillation (13). Only then can serial electric shock defibrillation (14) be attempted. Otherwise the heart will not be ready to respond by massage following electrical arrest. Occasionally, ventricular fibrillation may revert to a normal rhythm by massage alone (15).

The treatment of gas embolus requires the application of a simple manoeuvre conceived experimentally by Durant, Long and Oppenheimer (16) and subsequently attempted with success on humans by Hamby and Terry (17). It consists in placing the patient in the left lateral position. If this does not restore a normal heart beat, needle puncture of the right ventricle should be performed in an attempt to aspirate the air therein. If this fails a rapid thoracotomy and aspiration of air under direct vision should be attempted by the surgeon. If the heart remains stationary after aspiration, massage should be instituted.

The Control of Adequate Cardiac Massage

Cardiac massage will not produce an efficient artificial circulation unless it develops a palpable peripheral pulse and raises blood pressure to a level of 70 to 80 millimetres of mercury, synchronized with each passive systole. The immediate physiological response to efficient massage should be a reduction in mydriasis and improvement in the color of the patient, provided artificial respiration is effective.

When these conditions are realized, the time will be opportune for the anaesthetist to insert an endotracheal tube. This will prevent aspiration of air into the stomach and insure a clear airway.

Artificial respiration should continue until the return of a spontaneous and adequate respiration.

Massage should continue as long as it appears adequate and pupils are not fully dilated.

The Use of Drugs in Cardiac Arrest

We have already said a few words with regard to the prophylatic use of drugs.

The audacity and impulsiveness that seem to govern the injection of drugs directly into the heart chambers appear to originate from the impression that sustained cardiac massage will, in itself, prevent spontaneous recovery.

It is our sincere opinion that drugs, associated with massage, are more often responsible than massage alone for preventing return of spontaneous heart beat. Although we are not prejudiced against the use of drugs in cardiac arrest, we have purposely omitted discussion of their therapeutic use to emphasize our contention that they are the least important items in the treatment of cardiac arrest. Indeed mechanical and electrical means of cardiac resuscitation are gradually acquiring precedence over drug therapy. Although there is much room for improvement, great strides are being made as already evidenced by the electronic artificial pacemaker which has opened the possibility of successful simplified cardiac resuscitation.

Summary

After reviewing the main surgical and anaesthetic causes responsible for

sudden cardiac failure during surgery, prophylactic measures to prevent it are outlined.

Methods of diagnosis and procedures in treatment are suggested. Those will usually lead to successful resuscitation from clinical death, provided they are applied efficiently and diligently. Ill-timed use of drugs and hesitant attempts to restart a powerless heart are to be deplored.

Better results are obtained only when close co-operation exists between surgeon and anaesthetist.

Résumé

Un arrêt cardiaque en cours d'opération, quelqu'en soit la cause, peut être traité avec succès, sans séquelles, si l'intervalle de temps entre la cessation clinique des battements et de leur retour effectif ne dépasse pas environ quatre minutes.

Les manipulations chirurgicales, le choc, l'hémorragie, l'excitation de zônes réflexogênes, la dépression respiratoire, l'hypoxie, certains agents anesthésiques et bien d'autres facteurs peuvent être incriminés. Connaissant ainsi de nombreux éléments qui mènent à un arrêt cardiaque, tous les moyens de les éviter doivent être mis en œuvre. Ceci exige une collaboration constante et soignée de la part du chirurgien et de l'anesthésiste, qui travailleront de concert pour d'abord protéger le malade, chacun contribuant selon ses moyens, sans tenter de prouesses d'une valeur douteuse. Une oxygénation tissulaire aussi saturée que possible doit toujours être de rigueur.

L'arrêt du cœur impose un diagnostique immédiat, précis et son traitement doit éliminer une thérapeutique hésitante, sinon nuisible. La pulpart des drogues et les demi-mesures sont surtout à écarter. Le massage du cœur, par voie immédiate, et l'oxygénation au niveau pulmonaire constituent les éléments essentiels de la réanimation si l'on peut espérer en tirer un résultat satisfaisant.

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THE ANAESTHETIST'S ROLE IN THE CARE OF RESPIRATORY POLIOMYELITIS*

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RESPIRATORY poliomyelitis is becoming an increasingly great problem, both medical and economic, with wide implications over North America. There is an increasing incidence of the disease, and at times one would suspect greater virulence of the virus. Certainly it is no longer merely a children's disease. Figures are not prepared as yet for our 1953 epidemic, but in our own city there were more cases of adult respiratory poliomyelitis than children's cases. It is the belief of a few people that medical education and clinical methods pertaining to this dramatic and disastrous disease have not kept pace with the general advances in medicine in other fields and particularly have not made use of experts in the special fields of biochemistry, pathology, internal medicine, endoscopy, physical medicine and anaesthesia. In addition, other non-medical but important professional groups have not been employed or consulted to the optimum extent, namely the social or welfare case worker; the occupational therapist; the special school teacher; the pyschologist and psychiatrist; and the speech therapist. It is our belief now that poliomyelitis, whether spinal or bulbar in type, of whatever combination, can best be treated in an organized polio centre where the services of any or all of the specialists mentioned above are available at any time.

As for the Polio Centre itself, we believe that every effort should be made to have all patients under one roof throughout their course, with the possible exceptions of a few milder orthopaedic cases after the acute stage is over. This centralization in the long run is more efficient economically and physically for the many medical and social problems involved. A full-time director with sufficient medical staff to provide complete twenty-four hour coverage is mandatory. A person in the early stages of polio and one who requires a respirator has been likened to a patient on an operating table, under the influence of an anaesthetic, who deserves practically minute-to-minute observation and skilful care. The medical profession should no longer be content to merely "hope for the best" and relegate the care of these unfortunate people to nurses and orthopaedic specialists.

Management of Respiratory Insufficiency due to Poliomyelitis

The respiratory difficulties in polio are the result of multiple disturbances: dyspnoea, derangement of respiratory rhythm, bronchial hypersecretion and local vasomotor anomalies with oedema. All these contribute to varying pictures of asphyxia. Poliomyelitis has been mistaken for asthma, bronchopneumonia, pulmonary oedema of cardiac, renal or infectious origin, and commonly hysteria.

It is well known, of course, that no specific medication to combat the

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paralysis or the causative virus is available. At present, only mechanical devices for symptomatic treatment are available. We can, however, do much to prevent death by constant care and accurate clinical assessment of each case. Prior to 1929–30, the mortality from respiratory paralysis was practically 100 per cent. In 1945 it was still over 50 per cent. Since 1950 it has been reduced to 20, 15 and even 10 per cent, in some centres.

It is useful to consider that there are three main types of respiratory failure, although often combinations of these may occur in one patient:

1. Type due to paralysis of primary muscles of respiration—intercostals and diaphragm.
2. Type due to pharyngeal paralysis and resultant obstruction of the airway.
3. Type due to central disturbances—respiratory, vasomotor and vagal centres.

Type One. In those with simple paralysis, the pathology is easy to understand, and treatment is the use of a respirator. However mechanical respiration is very crude and is not a substitute for the intricate mechanisms normally regulating respiration. Ordinary biochemical tests available are too clumsy and too slow to be of practical value in the regulation of the mechanical respirators available in most hospitals. Until recently, astute clinical observation by the experienced operator, using trial and error settings, was the mainstay of management. In assessing the need for a respirator, a rough estimate of vital capacity may be had by asking the patient to count aloud slowly as far as possible with one breath. It is preferable to use some form of respiration meter or spirometer, which causes no effort, inconvenience or delay. Rising blood pressure, pulse and respiration rates, along with flaring of alae nasae, use of neck muscles, increasing anxiety, inability to sleep and of course cyanosis, are all signs which may indicate respiratory failure. On our admission or observation wards we keep a chart by the bedside, believing that, as in the operating theatre, a graph of frequent readings more readily indicates trends of the patient's condition. Such charts are also maintained in plain view beside each respirator and not concealed in the nurse's station. We have also found it important to have a card pasted near the controls of each machine, so that the respiratory rate, positive and negative pressures, tidal volume, and alveolar CO_2 estimations, can be entered daily or oftener and seen at a glance by all attendants. Fluid balance charts are likewise maintained.

Type Two includes those cases of pharyngeal paralysis (bulbar polio) and this group is much more difficult to deal with. There is often more likelihood of acute emergencies such as severe laryngospasm, or asphyxia from sudden aspiration. Laryngeal paralysis is rare but spasm is common. The majority in this group should have an early tracheotomy. Endotracheal equipment and bronchoscopes, to say nothing of experts in their use, should be within a few seconds' reach of bulbar patients. Some mild cases get by with only postural drainage, oral suction and "Lady Luck." All must have plenty of rest and yet be constantly watched.

Type Three includes those cases of involvement of the higher centres, respiratory, vasomotor, and vagal. This may be hard to detect and equally hard to treat. Vagal paralysis will produce tachycardia, an ominous sign. Irregular, jerking or hiccoughing respirations indicate central involvement and primitive

control. These patients do poorly in tank respirators because of inco-ordination and a tendency to "buck" the machine. We have tried the electrophrenic stimulator briefly but were discouraged by the technical difficulties. In its place, we have used "Flaxedil" as recommended by the Minneapolis group. This relaxing agent is relatively stable and free of histaminic effects. With the patient in a respirator, a curarizing dose can be given by the nurse about every half-hour using the intravenous drip. Adaptation to the respirator and hence more adequate pulmonary exchange are then possible. During such treatment, one must beware of severe changes in cardiocirculatory dynamics, especially if the patient is postured on the side.

Respirators

The tank-type is still the most efficient ventilator, having a potential of about twice the tidal air required. Some models have positive-pressure devices at the head and, used for short periods, facilitate physiotherapy or other procedures. None of these devices should be allowed to delay or prevent suction of secretions. Another improvement is a cam-type drive which produces a longer inspiratory phase and shorter, more expulsive expiration followed by a pause. This type of cycle is of more physiological benefit and promotes expulsion of secretions and greater comfort. Several other new features are being developed.

Of the "portable" respirators, the older chest-type of cuirass was uncomfortable and did not make enough use of the diaphragm and abdomen. Newer models employ larger, more comfortable shells, with a vastly improved mechanism and physiological cycle.

The "AGA Pulmospirator" from Stockholm is a very interesting and inexpensive positive pressure respirator which is actuated by compressed air or oxygen, thus avoiding the need of electric power which may be a serious difficulty in the transportation of patients from a distance. The pressure and duration of inspiratory and expiratory phases are readily adjustable.

The rocking-bed is not as efficient as the tank for pulmonary ventilation, but is very useful during recovery, in assisting in weaning from the tank, enabling better muscle tone and circulation in the body generally.

Tracheotomies

There is still a controversy over the tracheotomy, and a wide range of opinion: some would avoid it, others would apply it to every respiratory case and every bulbar case. In general, prime indications include inability to cough; inability to swallow; laryngeal stridor or croupy voice; and pulmonary oedema. The operation entails a calculated risk but this is usually much less than the risk of going without it. Tracheotomy has four advantages; (1) it promotes a free airway at all times; (2) it permits suctioning of tracheo-bronchial tree and greatly facilitates bronchoscopy; (3) it enables positive pressure devices to be used; and (4) if the tube is cuffed it prevents aspiration of foreign material.

In the Edmonton Isolation Hospital we have found vinyl ether satisfactory for small children, relatively small amounts being required to accomplish intubation. Older children and adults for whom local anaesthesia was not suitable, were given minimal amounts of thio-barbiturate and succinylcholine for rapid intubation, then nitrous-oxide-oxygen for maintenance. Many patients required full

or partial respiratory assistance because of the disease rather than the anaesthesia. In some centres the operation is carried out with a bronchescope in place, but we favoured a portex tube, believing that suctioning can be as good, adaptation for anaesthesia or assisted respiration is simpler, and toleration of the tube somewhat easier. Most authorities prefer not to premedicate, thus avoiding further depression of vital functions, and omit atropine in order to keep the secretions as thin and watery as possible.

The Minneapolis group have emphasized the need for using a large tracheotomy tube. Even a No. 7, the largest size, has only half the end-area of the adult trachea. Short sections of portex tubing with thin walls may be used in place of the standard silver tubes. The bevelled end must be smooth and of course not too long. It is essential to firmly suture the tying-tape to the tube to avoid slippage. Such a tube is easy to make, easy to adapt to positive pressure apparatus, can be changed easily, and causes minimum irritation.

The Problem of Regulating Optimum Respiratory Exchange

Clinical judgement based upon experience is important, but should be assisted by more objective methods. Much is rightly said about anoxia, but too little is said of CO_2 imbalance. Providing the lungs are normal, there will usually be adequate oxygen uptake in the presence of a reasonable minute volume. If extra O_2 is supplied, very slight respiratory movement may be sufficient to raise alveolar tension high enough that arterial blood will be nearly or completely saturated; but retention of CO_2 is presumed to occur in spite of the degree of O_2 saturation, and in the absence of cyanosis.

The importance of CO_2 retention is often demonstrated in respiratory poliomyelitis. On admission, patients frequently exhibit the picture of acute asphyxiation, with dyspnoea, stridor, inability to swallow, rigidity of muscles of respiration, cyanosis, tachycardia, and hypertension. When tracheotomy is done, the tracheobronchial tree cleansed, and normal ventilation restored, a rapid "wash-out" of CO_2 and immediate fall in blood pressure ensues. This picture is similar to that occasionally seen after cessation of a long, difficult or badly managed anaesthetic. In some patients, ventricular fibrillation and cardiac arrest have occurred. To prevent this catastrophe, the level of CO_2 should be slowly reduced over a period of twelve to twenty-four hours. This may be done with a partial rebreathing system or administration of small quantities of CO_2. Pulse and blood pressure must be charted and followed carefully. Early in our epidemic several cases of tetany occurred in the first few moments after tracheotomy or on the instigation of mechanical respiration. Another point is that a low CO_2 tension may prevent O_2 from leaving the red cells, and the tissues may thus be anoxic in the presence of fully saturated red cells. A CO_2 combining-power estimation is meaningless here, because there may be a normal value in the presence of a low CO_2 content.

We know that free CO_2 and blood bicarbonate constitute an important buffer system for keeping blood pH constant. With defective ventilation and CO_2 retention, changes in the pH may be manifested by elevation in blood pressure and alveolar CO_2 up to 8 or 10 per cent. With further retention, in the range of an alveolar CO_2 from 10 to 12 per cent, a narcotic effect occurs, with peripheral vasomotor collapse, coma, delayed cardiac conduction and bradycardia. Usually

anoxia is present as well. Such a state can occur insidiously in respirator cases from a multitude of mechanical and physiological causes.

To provide a practical basis for management, one should have a daily knowledge of air exchange (tidal air) and CO_2 content. Our work is based on the assumption that end-tidal samples of expired air are practically equivalent to alveolar air, and that CO_2 determinations thereon give sufficient information. This procedure eliminates the need for elaborate estimations such as blood pH determination and the solution of the Henderson–Hesselbach equation. Rice has devised an ingenious end-tidal sampling device, and a simple method of measuring the CO_2 percentage, both of which can be used quickly in the ward beside the patient. Details of his method will be published shortly.

Summary

An effort has been made to show that the anaesthetist is particularly qualified to assist with the assessment and management of respiratory poliomyelitis, and can contribute materially towards the scientific treatment of this disease. Time has not permitted a detailed discussion of the many facets of this interesting subject, but some of the physiological problems have been outlined and some practical suggestions given. An active poliomyelitis ward is recommended as a first-class laboratory for the study of respiratory physiology and electrolyte balance.

Résumé

Les difficultés respiratoires dans les cas de poliomyélite proviennent de troubles multiples: dyspnée, dérangement du rythme respiratoire, hypersécrétion bronchiale et anomalies vasomotrices locales avec œdème. Tout ceci contribue à former des cas variés d'asphyxie. On a comparé le malade atteint de poliomyélite dans les premiers degrés et celui dont l'état exige un poumon d'acier, au patient sur la table d'opération sous l'influence d'un anesthésique et nécessitant une observation incessante et des soins adroits. L'anesthésiste est particulièrement indiqué pour fournir les soins spéciaux réclamés par les problèmes respiratoires de ces malades.

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EPIDURAL ANAESTHESIA IN INFANTS AND CHILDREN*

F. G. Ruston, M.D.**

This is a report on the use of epidural anaesthesia in infants and children in the hospitals of Hamilton, Ontario, to the present date. Preliminary papers have been given at a Clinical Day programme in 1950 and again at a Sectional meeting of the Ontario Medical Association in May, 1952. I shall of course include material from those reports, although our technique has been modified since its first use in 1949.

After careful search of the literature, I have found only one reference to the use of this form of conduction anaesthesia in paediatric surgery. It is "Peridural Anaesthesia for Cystoscopy in the Child" by Roderic Sievers (1). In this paper the author also reports 21 cases in which "other operations were performed (four on the kidneys, six on the peripheral urinary paths, eight radical operations for hernia, and three appendectomies)." He used 1 per cent novocaine-suprarenin solution in amazing doses—15 cc. for a 5 kg. infant with an increase of 5 cc. for each 5 kg. to a maximum of 50 cc. for a 35 to 50 kg. person.

My interest in epidural anaesthesia was aroused while I was overseas with a Canadian Hospital, after reading Dogliotti's description of this segmental anaesthetic technique (2). I used this technique as often as I could, where it was feasible, especially for the poor risk group. As a result, when I was booked for a moribund infant with pyloric stenosis in 1949, I felt that epidural anaesthesia might be the answer. The result was so gratifying that I was encouraged to make further use of it for pylorics. Now several members of our staff are using this block anaesthetic. The number of anaesthetics is small, but enough have been given to see the application.

Anatomical Considerations

The epidural, peridural or extradural space is that portion of the vertebral canal which is not occupied by the dura mater and its contents. It separates the dura from the ligaments and the periostium which are the walls of the vertebral canal. Above, this space ends at the foramen magnum where the dura splits into two layers, one of which forms the endostium of the skull. Below, it is continuous with the sacral canal, terminating at the membrane across the caudal hiatus. Laterally, it communicates with the paravertebral tissues through the many intervertebral foramina and surrounds the dural sleeves which follow the nerves for varying distances. The epidural space contains loose areolar tissue, vascular plexuses, and fibrous extensions from the dura to the longitudinal ligaments. Usually there is a negative pressure which becomes more marked when the spine is flexed.

Method

I intend to discuss the thoraco-lumbar approach to the space. However, one

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must remember that there is also a caudal approach. In fact, one patient with severe imperforate anus was successfully anaesthetized by the caudal method. Originally procaine 1 or 2 per cent was used as the agent in these cases. However, since the introduction of xylocaine, we have used it to the exclusion of procaine, and only in the single dose method. The actual technique for epidural tap has been described by Dogliotti (2) and others, but when this is applied to infants, a difficulty arises from the diminutive structures and from the finer texture of tissues which are traversed by the needle point.

The following is the sterile kit we use for infants and children (Figure 1).

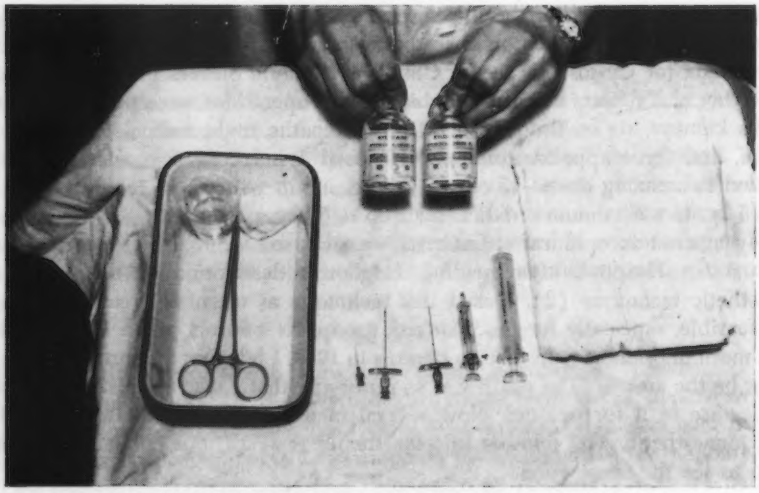

FIGURE 1. The kit used for epidural anaesthesia in infants.

There are two syringes, one 10 cc. and the other a 2 cc., two epidural needles and a hypodermic needle. Of course, there is a spinal sheet and a preparation tray. Xylocaine 1 per cent with and without epinephrine 1/100,000 is contained in rubber-stoppered vials. Since it is believed that 1/200,000 epinephrine is the safest solution to use (3), it is mixed in equal parts in the syringe. Xylocaine 2 per cent solution has been used for prolonged operations in the past, but I believe that a 1 per cent solution is adequate in most cases. Originally, a No. 20 short bevelled intravenous needle was used for the tap, but this was discontinued when the needle was found to be plugged after insertion into the interspinous ligament in two cases. Now we use a two-inch No. 22 gauge short bevelled spinal needle with added flanges and stillette. For children a No. 20 gauge is used. The hypodermic needle is for the skin wheal, and to place the hanging drop which will be described later.

In regard to preanaesthetic sedation, I believe that the schedule followed by Leigh and Belton (4) is adequate. We do not use morphine in infants and small children as there is a definite added risk in a training school hospital. Codeine in equivalent dosage is preferred. Also, a cut down should be done preoperatively

where indicated, although over half the pyloric stenosis cases in this series were treated without intravenous infusion. Furthermore, subcutaneous injections should not be started on the dorsal area, as this gives rise to oedema and makes the tap more difficult and hazardous.

The position in which the infant is held for the tap is very important. At first, the lateral position was used, but it was found that the infant frequently squirmed, making a fluidless tap more difficult. Finally, the sitting position was found to be the choice, for when the infant is clasped by the assistant with knees and elbows together little movement is possible. When this is done properly, the spine is nicely flexed and the spinal interspaces are readily palpable (Figure 2). Care must be taken not to obstruct breathing, especially in the presence of

FIGURE 2. The position of the child. The infant is clasped by the assistant with the elbows and knees together.

abdominal distention. The skin of the back is prepared and draped and the needle is placed with or without a skin wheal in a suitable interspace—usually between T10 and L1 for upper abdominal procedures, and L2 to L4 for a hernia or orthopaedic procedure involving the hip area. The needle is advanced well into the interspinous ligament, generally about ⅝ inch, and the stilette is removed. A drop of anaesthetic solution is placed over the hub of the needle with the hypodermic needle and syringe. Then the epidural needle is cautiously advanced and the action of the hanging drop is watched under a good light (Figure 3). One must be aware of the lessening of tissue resistance as the epidural space is entered. The hanging drop at this time is sucked into the needle. Rarely does one do a spinal tap if the drop is closely observed. In such an event the needle may be reinserted in another interspace. The desired amount of anaesthetic solution is then injected, the average infant receiving 5 to 6 cc. I used to inject 1 cc. and wait for five minutes to see if a spinal anaesthetic developed, but now I inject the

FIGURE 3. The "Hanging drop" in the needle hub is illustrated. This drop is sucked into the hub when the needle enters the epidural space.

full amount slowly but continuously because I believe that there is very little chance of piercing the dura when it is pushed away from the blunt needle point by the volume of anaesthetic fluid. Moreover, if the injection is prolonged, the chance of the infant's straining and forcing the dura against the needle is apparent. The needle is withdrawn and the puncture site sponged vigorously, as frequently one notices a slight leak of anaesthetic solution from the needle path. The infant is immediately placed in a supine position and restrained to a padded board by flannel bandages. Within a few minutes, there is definite evidence of decreased abdominal tone (Figure 4). Preparation and operation can be started within 5 or 10 minutes following the injection of the anaesthetic. If the infant is restless, a minute amount of pentothal may be given intravenously, or by catheter into the stomach, if a catheter has been passed to see if the stomach is empty. Nitrous oxide or light cyclopropane can also be given with a loosely placed infant's mask. Oxygen can also be given in this manner. Quite often the infant is content to suck the anaesthetist's finger—better still, an old-fashioned pacifier.

Clinical Cases

The following table shows briefly what we have done with epidural anaesthesia, alone and combined. The cases listed are those which I have done personally. Since this was written, I have used it for two more pylorics. Thirty-one additional pylorics and one duodenal atresia have been completed by other members of our staff, which brings the total to 77 cases.

Supplements were given to ensure there was no stirring of the shoulders or crying. Pentothal generally was for sedation effect. As you see, cyclopropane

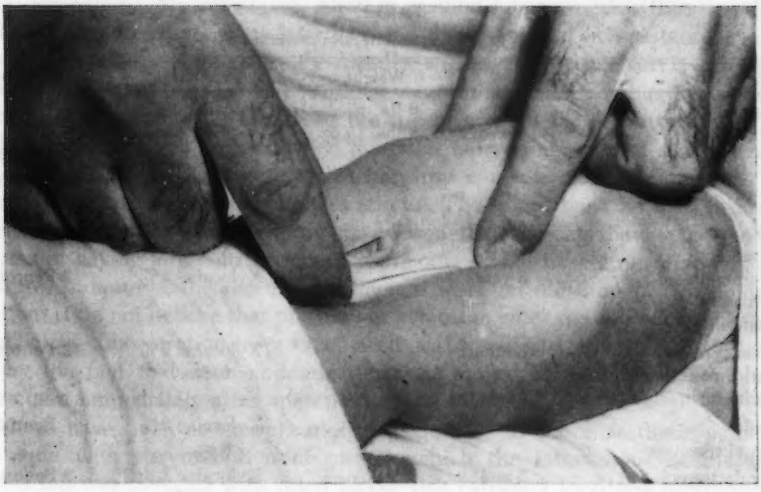

FIGURE 4. The abdominal wall is well relaxed and the pyloric tumour is evident.

was given only in cases where the segmental anaesthesia was inadequate. The complications could be attributed to the anaesthetic in only one case, and that was when there was a subcutaneous reaction to old blood which had plugged a needle. One patient was over-sedated, i.e., did not metabolize the sedative for twelve hours due to a ketosis and a middle ear infection. Two cases of convulsions could not be blamed on the xylocaine, for one followed definite over-loading of an infant with pyloric stenosis with transfusion and intravenous glucose and saline. The other convulsion developed with the breakdown of a gangrenous intussusception. In this case the convulsions were controlled by 4 cc. pentothal into the stomach and a twenty-minute apnoea developed in 5 minutes, showing how quickly the stomach will absorb pentothal. The infant with the volvulus was convulsing intermittently before operation and was moribund. The convulsions were controlled with intravenous pentothal and later with sodium luminal in the post-operative period. The only fatality was in the premature infant with jejunal atresia. This infant died three weeks after the last operation from further obstruction.

Discussion

It can be seen from the reference quoted above that epidural anaesthesia in infants and children is not a new thing. Perhaps it has been neglected in view of our present-day local anaesthetic drugs. Many hospitals do not have gas machines adaptable for use with infants and small children without a dangerous resistance to breathing and resultant build-up of CO_2. Certainly open ether in such cases is not without danger. Often the added risk of intubation is not justifiable. Some cases with associated respiratory infection or ketosis should have some form of conduction anaesthesia. I believe that epidural block, being a segmental anaesthesia, is more controllable in the infant than a spinal anaes-

TABLE I

USE OF EPIDURAL ANAESTHESIA

Operation	Age	Weight	Anaesthetic	Supplement
Pyloroplasty 20 cases	4 to 4 weeks	6 lbs. to 8 lbs. 15 oz.	8 Procaine 2% 3–5½ cc. 12 Xylocaine 1% 4½–6 cc.	2 N_2O 1 Cyclo 1 Pentothal 2 Pentothal 1 Cyclo
Hernia repair 2 indirect 2 strangulated 1 bilateral 1 umbilical	2 weeks to 3 years	8 lbs. to—	5 Xylocaine 1% 5–8 cc. 1 Xylocaine 2% 7 cc.	3 N_2O 2 Pentothal
Intussusception 2 with resections 2 without resections	3 months to 9 months		Xylocaine 2% 6–8 cc.	2 Pentothal
Volvulus Bowel resection	6 months		Xylocaine 2% 8 cc.	Pentothal
Appendectomy 2 gen. peritonitis	3 and 4 years		Xylocaine 1 & 2% 8 & 10 cc.	2 Pentothal
Splenectomy 2 for purpura	3 and 7 years		Xylocaine 1% 7 & 12 cc.	2 Pentothal
Laparotomy Large ovarian dermoid	20 months		Xylocaine 2% 8 cc.	Pentothal
Biopsy of liver malignancy	6½ months		Xylocaine 2% 7 cc.	
Jejunal atresia 2 operations	Premature 24 hours	4 lbs. 7 oz.	Xylocaine 2% 3½ cc.	
Duodenal stricture anastromosis			Xylocaine 1% 5 cc.	
Umbilical hernia Excision of lobe of liver	36 hours	7½ lbs.	Xylocaine 1% 5 cc.	
Congenital dislocation of hip	3 years		Xylocaine 2% 6 cc.	Pentothal
2 hip fusions T.B.	6 & 7 years		Xylocaine 2% 10 cc.	2 Pentothal

thetic. Procaine as an agent was unsatisfactory, as the time limit was too short. Xylocaine has overcome that difficulty. It is true that xylocaine (5) is not hydrolized but is excreted as such by the body and therefore could be considered more toxic than procaine. However, in actual practice, there has been no clinical evidence of an increased toxicity in infants and children. For adults, the continuous or intermittent catheter technique has been used with success elsewhere. Obviously this technique would be impossible in infants owing to the size of catheter. Furthermore, there is no need for an intermittent technique with xylocaine, for 1 per cent will last at least 1½ hours and 2 per cent at least 3 hours.

There is a definite need for skill in identifying the epidural space. Some of the early workers used the method of doing a spinal tap and withdrawing the needle one or two millimetres until there was no spinal fluid and then injecting a small amount of solution. If no spinal anaesthesia developed in 5 minutes, the remainder of the solution was injected. In several cases I have used this method and no

spinal anaesthesia has developed. Another method I have used is that described by Dogliotti and others. It is based on the disappearance of resistance against the plunger of the syringe as the needle with syringe attached is advanced through the interspinous ligament and ligamentum flavum and enters the epidural space. Macintosh (6) has described the use of a small balloon attached to the epidural needle which deflates when the point enters the epidural space. I have not used this. I feel that the disappearing drop is a safe and easy method. The needle must have a short bevel and a stilette. The infant must be held firmly in a flexed position. It has been my experience that patients having dependent oedema or having large intro-abdominal tumours do not have a negative epidural pressure. In spite of the recent experimental work on diffusion (7) of epidural solutions, I do not believe that procaine or xylocaine enter the subarachnoid space in sufficient concentration to produce a clinical spinal anaesthetic. This is borne out by the fact that each abdominal patient moved its feet when stimulated before and immediately after operation.

There have been no complications attributable to the anaesthetic agent or technique with the exception of one in which the intravenous needle used for the tap was plugged with dried blood; this caused a localized subcutaneous reaction, which resolved with treatment. There have been no convulsions or other toxic manifestations from the anaesthetic agents. There has been no evidence of neurological sequelae. Blood pressures have not been taken. Pulses have remained good in quality. Respirations have been quiet and unlaboured, not of the type so often seen with open ether. Relaxation has been truly remarkable. The post-operative course has been very satisfactory—even with the intussusceptions and the volvulus, which were desperate cases. Only a small number of infants with pyloric stenosis have required transfusion. There are two precautions to be taken, however; one is to maintain body temperature, and the other to keep the infant in a flat or slightly Trendelenburg position for three hours post-operatively, or until abdominal tone has returned to normal, in order to prevent pooling of blood in the visceral area and lower extremities.

The attitude of surgeons and paediatricians to this form of anaesthesia has been interesting. At first one could feel a slight scepticism, but they have since become agreeably impressed with its use in infant surgery so that now there is often a request for "one of those epidural blocks."

Epidural anaesthesia is a definite addition to the techniques applicable to paediatric anaesthesia. There is a certain risk which depends to a great degree on the skill of the anaesthesiologist. No one should attempt such an anaesthetic in an infant unless he has had considerable experience in adult epidurals. Just as an increased vigilance and skill are necessary for safe use of our modern adjuncts to general anaesthesia, so are awareness of and ability to cope with the hazards which may arise in this anaesthetic.

Summary

Epidural anaesthesia has been employed in 77 infants since 1949 for the operation of pyloroplasty, for other abdominal procedures such as intussusception, resection of bowel, hernial repairs, splenectomies and for operations on the hip joint. The agents were procaine 1 or 2 per cent in the earlier cases, and xylocaine 1 or 2 per cent with epinephrine 1/200,000 in later cases. The technique has

been satisfactory to anaesthetists and surgeons. The author's technique is described.

Résumé

Ce texte décrit l'expérience de l'auteur dans l'emploi de l'anesthésie épidurale chez les nourrissons et les enfants, de 1949 jusqu'à présent. Ce n'est que tout récemment que l'auteur a trouvé une référence dans les textes à son emploi antérieur.

Au début l'agent employé fut la procaïne, 1% ou 2%, remplacée plus tard par l'xylocaïne 1% ou 2% avec 1/200,000 d'épinéphrine. Des canules lombaires spéciales de 2 pouces, jauge No. 22 à biseau court furent employées. La méthode d'identification de l'espace épidurale fut celle de la goutte pendante qui disparaît dans le moyeu de la canule à cause de la pression négative dans l'espace épidurale. L'enfant est maintenu dans une position assise, par l'assistant, qui le tient coudes aux genoux, empêchant ainsi le mouvement de l'enfant. Le dosage moyen pour un enfant de 7 à 8 livres est de 5 à 6 cc d'xylocaïne 1% en dosage unique dans T10-L1 pour les opérations abdominales supérieures et dans L1-L4 pour les hernies et les procédés orthopédiques. L'anesthésie avec relâchement marqué s'ensuit en 10 minutes. Des agents anesthésiques supplémentaires furent le pentothal, le cyclopropane ou le protoxyde d'azote. Soixante-dix-sept épiduraux furent administrés avec une seule complication due à l'anesthésie et cela une réaction subcutanée causée par du sang coagulé provenant d'une canule bouchée avant l'emploi dans la technique de canules lombaires. La majorité des cas consistait en opérations sur le pylore (53) mais d'autres procédés abdominaux furent employés tels l'étranglement, l'excision de l'intestin, des réparations herniaires, la dissection de la rate et des opérations sur l'os de la hanche.

L'habileté de l'anesthésiste doit être grande pour empêcher l'injection intra-durable ou le dommage aux nerfs. Il faut être habile dans l'emploi de cette technique chez l'adulte avant de l'essayer chez l'enfant. Cette façon d'amener l'anesthésie est très utile lorsqu'il y a accompagnement d'infection respiratoire, ketosis, etc., et dans les cas où les machines à administrer le gas ne sont pas adaptables à l'anesthésie de l'enfant. Les chirurgiens sont contents à cause du relâchement maximum et de la respiration paisible des patients. Cependant il faut souligner qu'on doit veiller aux hasards de ce type d'anesthésie et savoir et pouvoir remédier avec efficacité aux complications.

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THE "COMPETITIVE" MUSCLE RELAXANTS*

S. L. VANDEWATER, M.D., F.R.C.P.(C)**

Pharmacological Review

The pharmacology of nerve impulse transmission at the neuromuscular junction and the effect of the various relaxant drugs should be understood by all who use these drugs. Curare is one of the few drugs which, in therapeutic doses, acts at one site only with a reversible pharmacological action. It is said to be "the most purely elective drug" known.

The muscle relaxants—d-tubocurare (d-tubocurarine), Flaxedil (gallamine triethoidide), Metubine (di-methyltubocurarine), Laudolissin—are grouped together because of their mechanism of action in producing striated muscle relaxation. It is postulated that there are specific acetylcholine (ACh) receptors, located in the motor-end plate region of muscle cells. These relaxants, mentioned above, also fit the configuration of these receptors, and thus occupy these receptors, preventing fixation of ACh and hence inhibiting the action of ACh. This is called substrate competition. The ACh which is present and "unfixed" because of the substrate competition by a relaxant drug is then hydrolysed by cholinesterase.

In the following discussion, I wish to bring out three points which are directly related to the clinical use of these drugs.

1. The degree of muscular relaxation depends not only upon the particular relaxant used, and the amount of the drug, but also upon the amount of ACh released as a response to nerve impulses received at the motor-end plate. Thus in the lighter planes of anaesthesia, which are commonly used today—i.e. 1st plane, 2nd stage (Guedel), or stage of anaesthetic sleep (Harris)—effector nerve impulses (rhythmic impulses from higher centres, which maintain normal muscle tone) are still present. Thus the amount of ACh present is greater than in the deeper planes of anaesthesia, and more relaxant is required to compete with the ACh to produce a given state of muscular relaxation. *Therefore* lighter planes of general anaesthesia require more relaxant.

2. The loss of muscle tone in skeletal muscles can be maintained for as long as the accumulation of an effective concentration of ACh at the neuromuscular junction is prevented. Thus if a patient be kept continuously anaesthetized to the level of complete sensory loss (between the second and third planes) a given degree of relaxation with one dose of d-tubocurarine can be maintained for up to five hours. Under these conditions the release of ACh is effectively prevented by the maintenance of anaesthesia to the level of complete sensory loss throughout. *Therefore* the depth of anaesthesia affects the duration of action of relaxants.

3. It is suggested that different muscle groups have different quantities of ACh formation at their respective neuromuscular junctions. Thus the small

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muscles of the eyes, mouth, etc., have less than the medium muscles (limbs), and they less than the flat muscles in the following order: abdominals, back, intercostals, and intercostal portion of the diaphragm, and finally the crural fibres of the diaphragm. The large limb and trunk muscles receive more effector impluses to maintain posture, and the crural fibres of the diaphragm receive the most as they are under continual bombardment from the respiratory centre. Thus one can see that various muscle groups will be paralysed to a different degree by a given dose of relaxant and as the depth of anaesthesia affects the amount of ACh present, *therefore*—the depth of anaesthesia affects the site of relaxation.

It is said that some relaxants, particularly Flaxedil and di-methyltubocurarine, spare the intercostals, yet at the same time give adequate abdominal relaxation. This is only a clinical impression, fostered particularly by the makers of the said drugs. It has never been proven, and I personally do not believe it.

Blood-borne anaesthetics do not depress the excitability or the conductivity of nerve fibres in concentrations used in clinical practice but they do reduce impulse formation in the upper motor neurons by brain depression. Impulse formation is not stopped completely but may be sufficient to be a major factor in complete loss of muscle tone, except in the crural fibres of the diaphragm. At the same time, the concentration of blood-borne anaesthetics at the neuromuscular junction may be sufficient to inhibit the small quantity of ACh released. This action enhances the action of relaxants and is particularly so of ether. There is some suggestion that hyperglycaemia inhibits ACh release, and this may be a factor with ether.

Natural Alkaloids versus Synthetic Relaxants

There has been a tendency in recent years to discredit the natural alkaloids, d-tubocurarine and its dimethylester, in favour of synthetic agents, Flaxedil, Mytolon and more recently Laudolissin. It must be remembered that most of the synthetic relaxants were developed in Great Britain and France because of the dollar problem since the United States controlled d-tubocurarine. Although we are all familiar with Flaxedil and have used it for about four years, it has only been used in the United States for the past year. As a rule the synthetic substances are cheaper than the natural alkaloids.

The argument against d-tubocurarine has been based on the so-called side reactions, the liberation of histamine causing bronchospasm, and, with large doses, hypotension, irreversible shock and C.N.S. depression. This was probably true in the early days of curare when the agent was not pure d-tubocurarine, but a mixture of alkaloids, curarines and curines. The present-day purified drug does not cause bronchospasm and in therapeutic doses, even such large ones as 50 to 60 mg., has no central effects except in the presence of anoxia and causes no cardiac depression, no change in cardiac output or in peripheral resistance. However, very massive doses will block autonomic ganglia (and perhaps all other relaxant drugs do likewise) and depress the vagus nerve. D-tubocurarine has no effect on liver, uterine or rental function and does not pass through the placenta.

Choice of Relaxant

Personally, I can see little difference in relaxing properties of these various drugs. Each drug enjoys enthusiastic support by certain groups and is in disfavour with others. From the conflicting reports of the superiority of one drug over another, one can only conclude that all the drugs are efficient and any differences noted are not due to the drug but to the manner in which it is used and the dosage.

Of all the drugs in this group, Mytolon has been the only one to fall by the wayside, because of its possible irritating and haemolytic properties. Some groups of anaesthetists use one drug exclusively for all purposes, but I believe it is better to use them all, and fit the drug to the specific purpose in mind, as they do have differences in time of onset of relaxation, duration of action, and miscibility with sodium thiopentone.

The details of dosage will not be mentioned. The duration of action varies somewhat, but, as pointed out above, this is greatly affected by the depth of anaesthesia, so that duration figures actually mean little. The onset of action does vary from ½ to 1½ minutes for Flaxedil, 2–4 minutes for di-methyl and d-tubocurarine, to 5 minutes for Laudolissin. Flaxedil does have a vagolytic action resulting in a varying degree of tachycardia, which is unimportant except perhaps in patients with cardiac disease. Because of this vagolytic action, Flaxedil has a tendency to depress the cough reflex and intubation with this relaxant may be smoother than with the others of the series.

All of the four drugs can be antagonized by prostigmine. This is a safe procedure if enough atropine (1/50 gr. for adults) is used 3–5 minutes before an adequate dose of prostigmine (2.5–5.0 mg.). All of these drugs except Laudolissin are miscible with thioperitone.

Laudolissin (Compound 20) is the newest of the drugs, not yet available on the market. It is a heterocylic decamethylene compound, and its structure is suggestive of a combination of d-tubocurarine and decamethonium. It was first described by Taylor and Collier in England in 1952. It is a true curarizing agent with a potency in man just one-half that of d-tubocurarine (whereas dimethylcurare is twice as potent). It has a somewhat longer action than d-tubocurarine and is antagonized by prostigmine. A dose of 30 mg. is roughly equivalent to 15 mg. of d-tubocurarine. Its onset of action is slower (5 minutes) and it has no "sparing" action on the intercostal muscles. It does not produce good vocal cord relaxation, unlike Flaxedil, and thus some other agent is better used for intubation purposes (succinyl choline is an excellent adjunct). It is said that "Syncurine" and Succinylcholine will reverse the effects of Laudolissin but this has not been my experience. There are no side effects with Laudolissin and it is not miscible with thiopentone.

Contra-Indications to the Use of Relaxant Drugs

1. Absolute—myasthenia gravis, and perhaps cases of motor neuron disease.
2. Relative

(*a*) *Age*: particularly in the elderly, poor risk patients, with decreased

metabolic rates; with children use reduced dosage, e.g. d-tubocurarine 1 mg./6 pd.; Flaxedil 1 mg./pd.

(*b*) Pulmonary emphysema and pulmonary fibrosis, where ventilation is dependent upon the action of the secondary respiratory muscles (scalenii, trapezii, etc.).

(*c*) Cardia disease. Flaxedil causes tachycardia and profound relaxation may reduce venous return and cardiac output in an already embarrassed cardiovascular system.

(*d*) Dehydration and vomiting, where potassium deficiency is suspected; it has been postulated that K^+ deficiency will prolong the action of relaxants.

Summary

The mode of action of the "Competitive" or "Blocking" relaxant drugs has been briefly reviewed. The degree of muscular relaxation obtained, the duration of relaxation and the site of relaxation are all affected by the depth of anaesthesia. Absolute and relative contra-indications to the use of relaxing drugs are briefly discussed.

Résumé

Les relâcheurs musculaires d-tubo-curarine, Flaxedil, Métubine et Laudolissine sont groupés parce que le mécanisme par lequel ils produisent un relâchement du muscle strié est identique. L'on postule qu'il y a des récepteurs spécifiques d'acétylcholine (ACh) situés dans la région de la plaque motrice des cellules musculaires. Ce groupe de relâcheurs s'adapte aussi à la configuration de ces récepteurs et en les "occupant" bloque l'action de l'ACh.

Le degré de relâchement musculaire, la durée du relâchement et l'endroit du relâchement maximum se rapportent inversement à la quantité d'ACh libérée dans la région des récepteurs de la plaque motrice, en réponse à l'excitation arrivant par les voies nerveuses. Etant donné que l'excitation est réduite par des plans plus profonds d'anesthésie, tout ceci est directement influencé par la profondeur de l'anesthésie. Une plus grande quantité du relâcheur est nécessaire pour une anesthésie plus légère, une quantité moindre pour une anesthésie profonde. La durée de l'action varie directement avec la profondeur de l'anesthésie.

Myaesthenia gravis est une contre-indication absolue à l'emploi de ces drogues. Des contre-indications relatives sont des extrêmes d'âge, un métabolisme diminué, l'emphysème pulmonaire ou fibrose, les maladies cardiaques, la déshydration et le vomissement.

CORRESPONDENCE

UNIVERSITY OF TORONTO
TORONTO 5, CANADA

DEPARTMENT OF ANAESTHESIA

The Editor,
Canadian Anaesthetists' Society Journal,
Toronto.

14th May 1954

DEAR SIR,

The Department of Anaesthesia of the University of Toronto is constantly receiving enquiries regarding the training program for Anaesthetists.

The great increase in hospital accommodation in Canada necessitates the training of an ever increasing number of certificated anaesthetists and the University of Toronto is providing more appointments in the two year course in Anaesthesia leading to certification and Fellowship.

In this two year course the post graduate student, who has already had at least a year in rotation interneship, serves as a senior interne in Anaesthesia for six-month periods in four of a group of hospitals comprised of the Toronto General, St. Michael's, Toronto Western, Toronto East General and the Hamilton General Hospitals, and the Hospital for Sick Children, Toronto. In addition the senior interne on a year's appointment to Sunnybrook Hospital (D.V.A.) is admitted to the course.

The anaesthetist-in-training registers in the Post Graduate School of the University, and attends lecture courses each year from September to June given by the Departments of Anaesthesia, Anatomy, Biochemistry, Dentistry, Medicine, Pathology, Pathological Chemistry, Pharmacology, Physiology and Radiology. He is also required to prepare papers for seminars and present cases at Staff meetings.

On the clinical side no medical centre provides a greater variety of surgical cases for anaesthesia than is presented in this combination of great hospitals closely connected with all the research departments of the University. In this connection there are also Fellowships available in the basic science departments in association with the department of Anaesthesia, where new drugs and techniques are studied from both the laboratory and clinical aspects. Appointments as clinical research fellow in the Department of Anaesthesia or as Resident Anaesthetist in one of the teaching hospitals are available to a limited number of applicants on completion of the two year formal course.

All enquiries should be directed to me at the University of Toronto.

Yours sincerely,
S. M. CAMPBELL, M.B., D.A., F.F.A.R.C.S.
Professor of Anaesthesia

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS

DR. Harold Griffith reports that plans for the World Federation of Societies of Anaesthesiologists are proceeding. He will attend a meeting of the Organizing Committee in Holland in June, at which reports will be received from national societies in the various countries and plans prepared for the Constituent Assembly of the new Federation. Up to the present, societies of anaesthesiologists in thirty different countries have approved the formation of the Federation and have made application for membership. It appears, therefore, that this will become a really representative organization of all the anaesthesiologists throughout the world.

It should be some satisfaction to Canadians to realize that their society is the third largest national group, and also that they have had an active share in the development of the World Federation. The purpose of the Federation as outlined in the Constitution is:

"To provide better anaesthesia for more people throughout the world."

It is hoped that this purpose may be achieved by setting up standards of training for anaesthesiologists; exchange of information regarding opportunities for training; assistance in the development of national societies in countries where anaesthesiology is in a very primitive state; and advising international and national government bodies on problems relating to anaesthesia.

The new Federation will be controlled entirely by anaesthesiologists, and will not have any official connection with governments, or the World Health Organization, or UNESCO.

The Constituent Assembly of the World Federation of Societies of Anaesthesiologists will be held at Scheveningen, near The Hague, September 5–10, 1955. The various national societies will send official delegates to this assembly. There will be held at the same time and the same place the first World Congress of Anaesthesiologists sponsored by the new Federation. The programme for this World Congress is now being prepared with the Netherlands Society of Anaesthesiologists as hosts. There will be a comprehensive scientific programme, and much opportunity for pleasant social diversion. It is hoped that there will be large delegations present from Canada, the United States and the other English-speaking countries. English will be the official language of the Congress, as well as the World Federation. Mr. W. A. Fentener van Vlissingen, Nederlandes Anaesthesisten Vereniging, BILTHOVEN, Holland, has been appointed Executive Secretary of the World Congress of Anaesthesiologists and he will be pleased to send information regarding plans for the Congress to anyone who is interested.

FEDERATION MONDIALE DES SOCIETES D'ANESTHESISTES

Le Dr. Harold Griffith rapporte que le projet d'établissement d'une Fédération Mondiale des Sociétés d'Anesthésistes se poursuit. Il assistera à une réunion du comité d'organisation en Hollande au mois de juin, réunion à laquelle des rapports seront reçus des sociétés nationales des divers pays et des plans seront établis pour l'Assemblée Constituante de la nouvelle fédération. Jusqu'à présent les sociétés d'anesthésistes de trente pays différents ont approuvé la création d'une fédération et ont demandé à être admises comme membre. Il semble donc que cette Fédération deviendra une organisation vraiment représentative de tous les anesthésistes à travers le monde.

Les Canadiens seront heureux de constater que leur société est par ordre d'importance numérique le troisième des groupes nationaux et aussi qu'ils ont eu une part active au développement de la Fédération Mondiale. Le but de cette Fédération est établi dans la constitution comme suit:

"Fournir une meilleure anesthésie pour un plus grand nombre à travers le monde."

On espère que ce but sera atteint par l'établissement de normes pour la formation d'anesthésistes; par l'échange de renseignements concernant les occasions d'entraînement; par l'assistance au développement de sociétés nationales dans ces pays où l'anesthésie est dans un état encore très primitif; et en conseillant les organismes gouvernementaux, internationaux et nationaux sur les problèmes relatifs à l'anesthésie.

La nouvelle fédération sera contrôlée entièrement par des anesthésistes et n'aura aucun rapport officiel avec les gouvernements ou l'Organisation Mondiale de l'Hygiène ou l'UNESCO.

L'Assemblée Constituante de la Fédération Mondiale des Anesthésistes aura lieu à Scheveningen près de La Haye du 5 au 10 septembre, 1955. Les diverses sociétés nationales enverront des délégués officiels à cette assemblée. A la même époque et au même endroit aura lieu le premier Congrès Mondial d'Anesthésistes, une initiative de la nouvelle fédération. Le programme pour ce Congrès Mondial est maintenant en voie de préparation, la Société d'Anesthésistes de Hollande agissant en capacité d'hôte. Il y aura un programme scientifique complet et beaucoup d'occasions de divertissements agréables. On s'attend à ce qu'il y ait de grandes délégations du Canada, des Etats-Unis et des autres pays de langue anglaise. L'anglais sera la langue officielle du Congrès et de la Fédération Mondiale. M. W. A. Fentener van Vlissingen, Nederlandes Anaesthesisten Vereniging, BILTHOJEN, Hollande, a été nommé secrétaire-exécutif du Congrès Mondial et il sera heureux de transmettre des renseignements au sujet des plans pour le Congrès à tous ceux qui s'y intéressent.

BRITISH MEDICAL ASSOCIATION MEETING

Toronto, 19–25 June, 1955

The British Medical Association will be meeting conjointly with the Canadian Medical Association in Toronto from June 19 to June 25, 1955. The meeting will follow the B.M.A. pattern. Amongst the Sections to be represented in the programme is the Section of Anaesthesia. The following officers have been appointed for the Section of Anaesthesia by Dr. T. C. Routley, President-Elect of the British Medical Association:

President: Professor R. R. Macintosh, Oxford

Vice-Presidents: Dr. G. S. W. Organe, London
Dr. George Cousineau, Montreal
Dr. Harry J. Shields, Toronto
Dr. B. C. Leech, Regina

Secretary: Dr. R. A. Gordon, Toronto

Asst. Secretaries: Dr. Shirley Fleming, Toronto
Dr. S. L. Vandewater, Toronto

The Secretary would be pleased to receive suggestions for the programme from Canadian Anaesthetists, as well as the names of British Anaesthetists whom their Canadian colleagues might wish particularly to have included in the programme.

REPORTS OF MEETINGS

Ontario Division Meets at Ottawa

A very interesting and well-balanced programme was presented at the Ontario Divisional Meeting held at the Château Laurier, Ottawa, on Saturday and Sunday, April 3 and 4.

The morning was spent visiting the Ottawa Civic Hospital where clinical demonstrations were given in the operating rooms.

Following luncheon, the afternoon session included the following papers:

1. Epidural Anaesthesia in Infants and Children. *By* Dr. F. Ruston, Hamilton.
2. Infant Anaesthesia in the Community Hospital. *By* Dr. V. A. Nekus, Kingston.
3. Spinal Anaesthesia in Obstetrics. *By* Dr. Best, Hamilton.
4. The Present Status of Spinal Anaesthesia. *By* Dr. C. R. Stephen, Durham, North Carolina.

During the day, the wives of the visiting anaesthetists were royally entertained by the Ottawa ladies. A very enjoyable banquet was held at the Château Laurier on Saturday evening.

The following morning was occupied largely by a Round Table discusssion, the title of which was, "Choosing the Proper Muscle Relaxants." Members of the panel included Dr. Stuart Vandewater, Toronto; Dr. William Cullen, Montreal; and Dr. Alan Noble, Kingston.

Many complimentary remarks were heard concerning this meeting. The papers were not too long, were well presented, and ample time was allowed for a thorough discussion of each subject. The active, good-natured participation of a great many of the audience resulted in very stimulating sessions. The fact that the programme was not a crowded one allowed ample time for discussion of controversial questions in detail, and we would do well to hold other meetings of this type.

A large number of commercial exhibitors were present and made a very valuable contribution to the meeting.

Doctors Bob Stringer and Ralph Probert of Hamilton are to be congratulated for their excellent programme. The committee on local arrangements was headed by Dr. Gordon MacKenzie of Ottawa, and we thank them most sincerely for their excellent hospitality.

Quebec Division Meeting

"A Day of Paediatric Anaesthesia" was the topic of the spring meeting of the Quebec Division of The Canadian Anaesthetists' Society held at the Children's Memorial Hospital, Montreal, on Saturday, April 10.

During the morning clinical demonstrations of various techniques for different age groups and different operations were conducted; also, practical instruction in pontocaine-aerosol administration for bronchoscopy, and the use of nitrous oxide and trichlorethylene for dental extractions.

Following a luncheon served at the Children's Memorial Hospital, the afternoon session commenced with the presentation of the following papers:

1. Anaesthesia for Infants in Every Day Surgery. *By* Dr. V. A. Nekus, Kingston, Ontario.
2. Attention to Details in Paediatric Anaesthesia. *By* Dr. H. M. Slater, Montreal.
3. Pre- and Post-operative Care in Children. *By* Dr. R. H. Ferguson, Montreal.
4. Poliomyelitis and the Anaesthetist. *By* Dr. Nicholson, Montreal.

Of particular interest were the scientific and commercial exhibts of paediatric anaesthesia equipment.

The meeting was concluded with a dinner held at the Montreal Club.

Nova Scotia Division Meeting

The Annual Meeting of the Nova Scotia Division was held in Halifax at the Naval Hospital, H.M.C.S. *Stadacona*, on Thursday, April 29, 1954. Surgeon Commander Harvey Little gave talks on "A Pentothal-Syncurine Mixture for Intubation" and on "Xylocaine in Regional Anaesthesia."

The following executive officers were elected by the Division:

Chairman: Dr. George D. Donaldson
Secretary: Dr. R. A. Paul Fleming

OBITUARY

Jean-Charles Doucet
(1902–1954)

Doctor Jean-Charles Doucet, whose premature death occurred suddenly on May 1, 1954, at his home in Montreal, had been a devoted associate in the Department of Anaesthesia at Notre Dame Hospital during the past quarter-century.

After brilliant studies at Valleyfield College, where he obtained a B. L. degree, he entered Medicine at the University of Montreal, graduating with honours in 1929.

His innate godliness and meekness always concealed a deep-rooted desire for lofty achievements and an unswerving devotion to duty.

In 1930, Doctor Doucet went to Toledo, Ohio, to study under Dr. McKesson. Following his return to Montreal, he spent more time under the tutelage of Drs. Bourne and Griffith, acquiring scientific background and confidence which were to put within reach a cherished ambition: to help his fellow-men, and this in the new specialty of anaesthesia.

At that time, Notre Dame Hospital was in quest of industrious, enthusiastic and promising young doctors. Jean-Charles Doucet was selected to be amongst those. To the Department of Anaesthesia he gave his very best, a dedication without stint. Subsequently, he became Assistant Professor of Anaesthesiology at the University of Montreal and was made a Fellow of the International College of Anaesthetists in 1937.

An extremely unfortunate accident in his youth had added to his gentle character a certain timidity, made all the more attractive by the affection which he displayed towards patients, colleagues and all those who enjoyed the pleasure of his association and friendship.

The Canadian Anaesthetists' Society, Notre Dame Hospital and all his comrades in Anaesthesia are losing a loyal, sincere friend and a personality who has left his mark in the organization of the specialty of Anaesthesia in Montreal. Thanks to his considerate help and advice, many stumbling-blocks were avoided; his gentle and calm mediation quietly found a solution to several difficult problems facing the profession.

Jean-Charles Doucet served the cause and the progress of Anaesthesia in Montreal with genuine distinction. His colleagues will be deeply affected by his loss and will miss the perfect gentleman and devoted collaborator he always was to all who had the privilege and pleasure of knowing him.

Confrère

ANAESTHESIA

Published for The Association of Anaesthetists of Great Britain & Ireland

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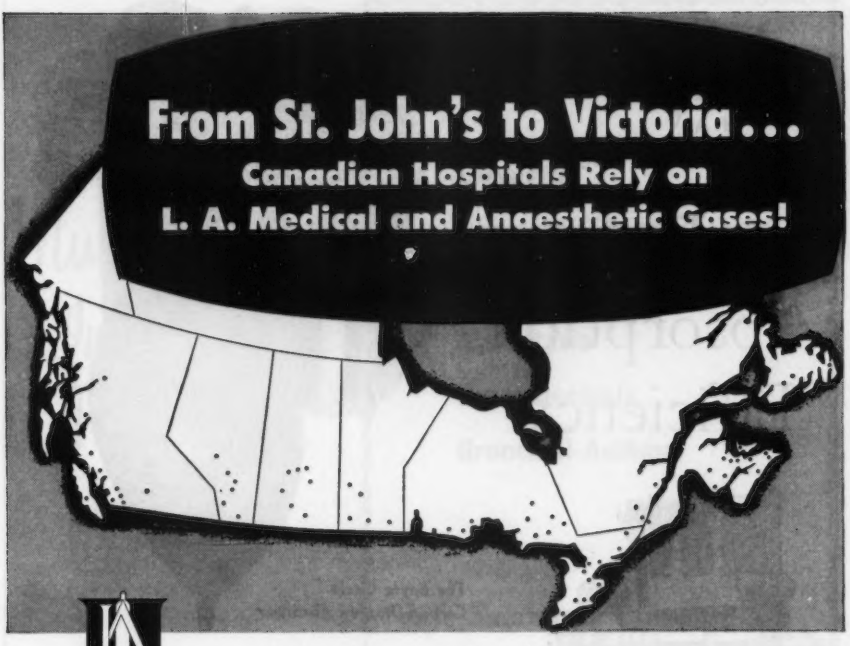

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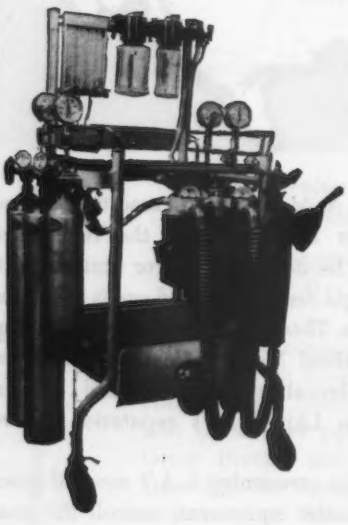

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Manuscripts

Articles should be typewritten in double space on one side of the paper only. Pages must be serially numbered, and each page should carry at its head the name of the author and the title of the article in full or in an appropriate abbreviation. The article should be concluded by a summary which will be intelligible without reference to the main text. All articles should be accompanied by a résumé presenting the important features in short form, for translation into the French language. French-speaking authors should provide this résumé in the French language.

References to the literature should be clearly indicated in the text by arabic numerals in brackets, thus (4). They should be set out in numerical order at the end of the article, typed in double space, as follows:

4. Griffith, H. R. & Johnston, G. E. The Use of Curare in General Anaesthesia. Anesthesiology 3: 481 (1942).

References to books will state in order: Name of Author, Title of Book, Edition, Place of publication, Publisher, Year of Publication, such as:

Labat, G. Regional Anesthesia. 1st ed., Philadelphia: Saunders (1922).

The names of all authors will be given in the first instance in each reference. In further references to the same authors the abbreviated form "Griffith *et al.*" may be used.

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